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, 2021

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

For the transition period from _____ to _____

Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

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

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

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

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

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

Indicate by check if the Registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the Registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

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

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

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

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

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

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

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The Nasdaq Global Select Market was $4,675,204,973 as of June 30, 2021.*

The number of shares of voting common stock outstanding as of February 16, 2022 was 141,688,727.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 20, 2022 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 2, 2022 are incorporated by reference into Part III of this Report.

* Excludes 23,819,152 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, 2021. 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), eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, tofersen and our technologies and products in development. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact of COVID-19 could have on our business, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

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

Summary of Risk Factors

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

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

TRADEMARKS

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

CORPORATE INFORMATION

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

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, or SEC. Periodically, we provide updates about the company in the Newsroom section of the Investors & Media page of our website. Any information that we include on or link to our website is not a part of this report or any registration statement that incorporates this report by reference. The SEC maintains an internet site, *www.sec.gov*, that contains reports, proxy and information statements that we file electronically with the SEC.

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2021
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PART I

Item 1. Business

Overview

We are a leader in RNA-targeted therapeutics. We believe our medicines, which are based on our novel antisense technology, have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases. We currently have three marketed medicines-SPINRAZA, TEGSEDI and WAYLIVRA. We also have a rich late-stage pipeline of medicines, primarily focused on our cardiovascular and neurology franchises. Our late-stage pipeline consists of six medicines in Phase 3 development for eight indications.

Over the past year, we made important progress toward achieving our goal to be a leading fully integrated biotechnology company. We advanced our commercial strategy and go-to-market plans for our near-term commercial opportunities, eplontersen, olezarsen and donidalorsen. We entered an agreement with AstraZeneca to jointly develop and commercialize eplontersen. We believe this agreement positions eplontersen to maximize value for patients and shareholders while also enabling us to bolster our commercial organization and accelerate our preparations for our near-term product launches.

We continued to advance and expand our Phase 3 pipeline with the achievement of key enrollment milestones for eplontersen and pelacarsen, and the addition of two new Phase 3 programs for olezarsen and donidalorsen, bringing us to 6 medicines in Phase 3 development addressing 8 indications. In 2021, we also reported data from the Phase 3 VALOR study of tofersen in patients with SOD1-ALS. While VALOR did not achieve statistical significance in the primary endpoint, signs of reduced disease progression were observed across multiple secondary and exploratory endpoints. Biogen is actively engaged with regulators to determine the next steps for tofersen. In addition, Roche recently announced plans to initiate a new Phase 2 study of tominersen in patients with Huntington's disease, based on new findings from a post hoc analysis of the Phase 3 GENERATION HD1 study of tominersen.

Our mid-stage pipeline also continued to perform well, with positive data readouts from several medicines. And we invested in expanding the reach of our technology, including obtaining exclusive rights to Bicycle Therapeutic's peptide technology targeting transferrin receptor 1 to expand the capabilities of our Ligand Conjugated Antisense, or LICA, technology. We strengthened our financial position and focused our resources in support of our highest priority programs through the integration of Akcea Therapeutics and our distribution agreements with Swedish Orphan Biovitrum AB, or Sobi. We accomplished all this and exceeded our 2021 financial guidance, including achieving revenues of $810 million. And we remain well capitalized with a 2021 year-end cash balance of $2.1 billion.

Our multiple sources of revenue and strong balance sheet enable us to invest in our strategic priorities to build our commercial pipeline, expand and diversify our technology and deliver new medicines to the market. By continuing to focus on these priorities, we believe we are well positioned to drive future growth and to deliver increasing value for patients and shareholders.

Marketed Medicines

SPINRAZA is the global foundation-of-care for the treatment of patients of all ages with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Biogen, our partner responsible for commercializing SPINRAZA worldwide, reported that as of December 31, 2021, over 11,000 patients were on SPINRAZA therapy in markets around the world. From inception through December 31, 2021, we have earned more than $1.6 billion in revenues from our SPINRAZA collaboration, including nearly $1.2 billion in royalties on sales of SPINRAZA.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with polyneuropathy caused by hATTR, a debilitating, progressive, and fatal disease. We launched TEGSEDI in the U.S. and the European Union, or EU, in late 2018. In 2021, we began selling TEGSEDI in Europe through our distribution agreement with Sobi. Additionally, in the second quarter of 2021, Sobi began distributing TEGSEDI in the U.S. and Canada. In Latin America, PTC Therapeutics International Limited, or PTC, is commercializing TEGSEDI in Brazil and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine that received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA in Europe through our distribution agreement with Sobi. Through our exclusive license agreement with PTC, PTC is working to provide access to WAYLIVRA across Latin America, beginning in Brazil. In the third quarter of 2021, the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária), or ANVISA, approved WAYLIVRA in Brazil. In December 2021, PTC submitted an application to ANVISA for approval of WAYLIVRA for the treatment of familial partial lipodystrophy, or FPL, in Brazil. If approved, Waylivra will be the first approved treatment for patients with FPL in Brazil.

Under our distribution agreements with Sobi, we retained the marketing authorizations for TEGSEDI and WAYLIVRA. We will continue to supply commercial product to Sobi and manage regulatory and manufacturing processes, as well as relationships with key opinion leaders. We will also continue to lead the TEGSEDI and WAYLIVRA global commercial strategy. In connection with the agreements, we restructured our European operations in the first quarter of 2021, and we restructured our North American TEGSEDI operations in the second quarter of 2021.

Medicines in Phase 3 Studies

We currently have six medicines in Phase 3 studies for eight indications, which include:

- Eplontersen: In July 2021, we achieved full enrollment in the NEURO-TTRansform Phase 3 study with data expected mid-2022. Enrollment is ongoing in the CARDIO-TTRansform Phase 3 study
  - In November 2021, we entered into an agreement with AstraZeneca for eplontersen, under which we will jointly develop and commercialize eplontersen in the U.S. AstraZeneca has exclusive rights to commercialize eplontersen in the rest of the world
- Olezarsen: We initiated the Phase 3 CORE study in patients with severe hypertriglyceridemia, or SHTG, in October 2021. Enrollment is ongoing in the BALANCE Phase 3 study in patients with FCS
  - Data from the Phase 2 study of olezarsen in patients with moderate hypertriglyceridemia and at high risk for or with established cardiovascular disease were published in the *European Heart Journal*
- Donidalorsen: Based on positive topline data from a Phase 2 study of donidalorsen in patients with hereditary angioedema which we reported in April 2021, we initiated the Phase 3 OASIS-HAE study in November 2021
  - We reported additional positive results from the Phase 2 study of donidalorsen at the ACAAI annual scientific meeting in November 2021, demonstrating rapid and sustained reductions in HAE attacks with favorable safety and tolerability
- ION363: In April 2021, we initiated a Phase 3 study in patients with amyotrophic lateral sclerosis, or ALS, with mutations in the fused in sarcoma gene, or FUS, or FUS-ALS, the most common cause of juvenile-onset ALS
- Pelacarsen: In August 2021, Novartis achieved 50 percent enrollment in Novartis' Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with established cardiovascular disease and elevated lipoprotein(a), or Lp(a)
- Tofersen: In October 2021, Biogen reported that tofersen did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring tofersen were seen across multiple secondary and exploratory measures of disease activity and clinical function
  - Biogen is actively engaging with regulators, the medical community, patient advocacy groups and other key stakeholders around the world to determine potential next steps
  - Given the high unmet medical need, Biogen expanded its ongoing early access program, or EAP, to the broader SOD1-ALS population
  - The Phase 3 ATLAS study in patients with presymptomatic SOD1-ALS is ongoing

COVID-19

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

Our Marketed Medicines – Potentially Transformational Medicines Bringing Value to Patients Today

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

SPINRAZA continues to demonstrate substantial benefit in SMA patients of all ages, supporting its position as a global foundation of care for the treatment of SMA. Biogen, our worldwide commercial partner, reported that as of December 31, 2021, there were more than 11,000 patients on SPINRAZA therapy.

SMA is characterized by loss of motor neurons in the spinal cord and lower brain stem, People with SMA have a deletion or defect in their *SMN1* gene and rely on their *SMN2* gene to produce functional SMN protein, which motor neurons need to maintain motor function and muscle strength. However, the *SMN2* gene can only produce approximately 10 percent of the SMN protein critical for motor neurons, resulting in severe and progressive loss of motor function and strength.

The rate and severity of degeneration varies depending on the amount of functional SMN protein a patient can produce. Type 1, or infantile-onset, SMA is the most severe form of the disease. Type 1 SMA patients produce very little SMN protein and often progress to death or permanent ventilation by the age of 2. Patients with Type 2 or Type 3, or later-onset, SMA produce more SMN protein, but also suffer from a progressive loss of muscle strength and function and a reduced life expectancy.

Biogen continues to expand the body of evidence supporting SPINRAZA's durable efficacy and well-established safety profile to address the remaining needs of SMA patients of all ages. In the Phase 2/3 DEVOTE study, Biogen is evaluating the safety and potential to achieve increased efficacy with a higher dose of SPINRAZA compared to the currently approved dose. At the AAN 2021 Virtual Annual meeting in April 2021, Biogen reported that initial findings from the DEVOTE study suggest no new safety concerns and support continued development of a higher dose of SPINRAZA.

In January 2021, Biogen initiated the Phase 4 RESPOND study evaluating the benefit of SPINRAZA in infants and children with a suboptimal clinical response to the gene therapy, onasemnogene abeparvovec.

And in September 2021, Biogen initiated the Phase 3b ASCEND study designed to evaluate the clinical outcomes and assess the safety of a higher dose of SPINRAZA in children, teens and adults with later-onset SMA following treatment of risdiplam.

Additionally, Biogen continues to conduct the Phase 2 NURTURE study, an open-label study investigating the benefit of SPINRAZA when administered before symptom onset in patients genetically diagnosed with SMA, and likely to develop Type 1 or Type 2 SMA. NURTURE was the first study to investigate the potential to slow or stop SMA disease progression in presymptomatic SMA patients. In June 2021, Biogen reported data from an interim analysis, showing that all study patients remain alive without the need for permanent ventilation. Additionally, at the time of the interim analysis, 92 percent of patients maintained the ability to swallow.

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

TEGSEDI – TEGSEDI (inotersen) injection is an RNA-targeted medicine indicated for the treatment of polyneuropathy due to hATTR in adults. TEGSEDI prevents the creation of TTR proteins, reducing the amount of amyloid that builds up, which damages organs and issues.

Polyneuropathy due to hATTR is caused by the accumulation of misfolded mutated TTR protein in the peripheral nerves. Patients with polyneuropathy due to hATTR experience ongoing debilitating nerve damage throughout their body resulting in the progressive loss of motor functions, such as walking. These patients also accumulate TTR in other major organs, which progressively compromises their function and eventually leads to death within five to fifteen years of disease onset. There are an estimated 40,000 patients with polyneuropathy due to hATTR worldwide.

TEGSEDI is commercially available in numerous countries, including the U.S., many European countries, Canada, and Latin America. In 2021, we began selling TEGSEDI in Europe through our distribution agreement with Sobi. Additionally, in the second quarter of 2021, Sobi began distributing TEGSEDI in the U.S. and Canada. In Latin America, PTC through its exclusive license agreement with us, is commercializing TEGSEDI in Brazil and is working to achieve access in additional Latin American countries.

The approvals of TEGSEDI were based on efficacy and safety data from the Phase 3 NEURO-TTR study in patients with hATTR amyloidosis with stage 1 and stage 2 polyneuropathy. We also conducted an OLE study in patients with hATTR treated with TEGSEDI to evaluate the long-term efficacy and safety profile of TEGSEDI. We reported interim data from the study that demonstrated continued efficacy in patients after two years. Results also showed that patients who started treatment earlier achieved greater long-term disease stabilization compared to those who switched from placebo to TEGSEDI in the OLE study.

WAYLIVRA – WAYLIVRA (volanesorsen) is an antisense medicine indicated as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. WAYLIVRA reduces triglyceride levels by inhibiting the production of apolipoprotein C-III, or apoC-III, a protein that is a key regulator of triglyceride levels.

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

WAYLIVRA is commercially available in multiple European countries and in Brazil. In 2021, we began selling WAYLIVRA in Europe through our distribution agreement with Sobi. In Latin America, PTC through its exclusive license agreement with us, is commercializing WAYLIVRA in Brazil and is working to achieve access in additional Latin American countries.

WAYLIVRA's conditional marketing authorization in the EU and approval in Brazil were based on efficacy and safety data from the Phase 3 APPROACH study, the ongoing APPROACH OLE study and supported by results from the Phase 3 COMPASS study.

Drug Discovery and Development

Introduction to Drug Discovery

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

Our Pipeline

We are a leader in the discovery and development of RNA-targeted therapeutics. We are focused on pioneering new markets and changing standards of care with a focus on cardiovascular and neurological diseases. Additionally, we are developing a number of medicines that are outside these areas. We also have an emerging specialty rare disease pipeline comprised of medicines which we believe represent a compelling opportunity for us. We are developing our medicines for systemic and local delivery (e.g., subcutaneous, intrathecal, intraocular, oral and aerosol). We plan to continue adding new investigational medicines to our pipeline in the future.

We have built a rich pipeline of medicines designed to treat many serious diseases. To select the best candidates, we efficiently screen many targets in parallel and apply our rational approach to selecting disease targets. With our expertise in discovering and characterizing novel antisense medicines, our scientists can optimize the properties of our antisense medicines against each particular target. We have created LICA technology, which we designed to enhance the effective uptake and activity of our medicines in particular tissues. With our LICA technology we attach specific chemical structures or molecules to our antisense medicines. With our first LICA conjugate, a complex sugar-like molecule called N-acetylgalactosamine, or GalNAc, we have shown an increase in medicinal potency of 20-30-fold for liver targets, compared to non-conjugated antisense medicines. Many of the medicines in our pipeline are LICA medicines, including four LICA medicines currently in Phase 3 studies: eplontersen, olezarsen, donidalorsen and pelacarsen. We have utilized our chemistry advancements to expand the therapeutic and commercial opportunities of our pipeline. Our antisense technology, along with our manufacturing and analytical processes that are the same across our medicines, shorten our timeline from initial concept to the first human dose, when compared to early development timelines for other drug modalities like small molecule and monoclonal antibody medicines.

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

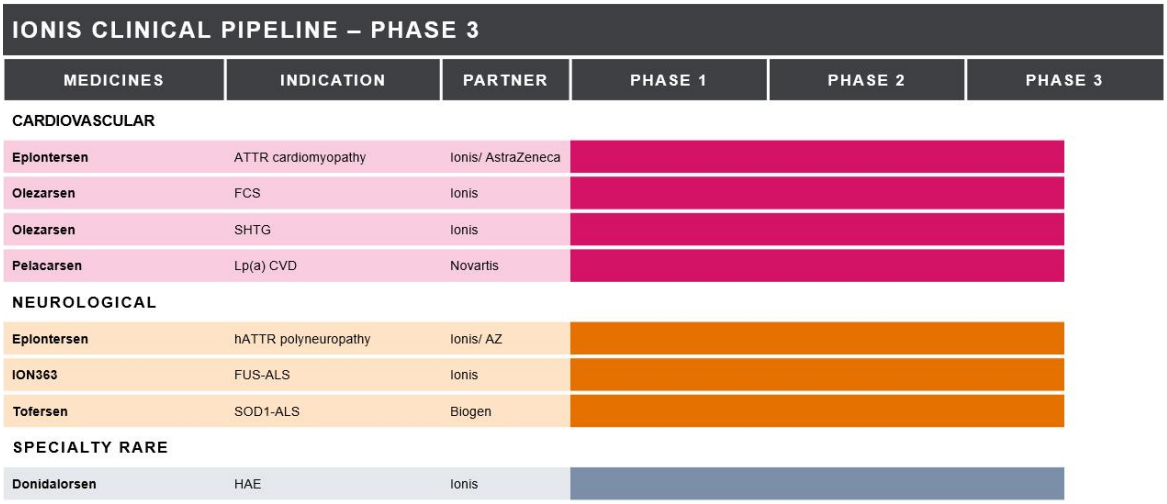
IONIS CLINICAL PIPELINE

MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
CARDIOVASCULAR					
Eplontersen	ATTR cardiomyopathy	Ionis/ AstraZeneca			
Olezarsen	FCS	Ionis			
Olezarsen	SHTG	Ionis			
Pelacarsen	Lp(a) CVD	Novartis			
ION449 (PCSK9)	CVD	AstraZeneca			
Fesomersen (FXI)	Clotting disorders	Bayer			
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension	Ionis			
IONIS-AGT-L_{Rx}	HF	Ionis			
NEUROLOGICAL					
Eplontersen	hATTR polyneuropathy	Ionis/ AstraZeneca			
ION363	FUS-ALS	Ionis			
Tofersen	SOD1-ALS	Biogen			
ION373 (GFAP)	Alexander disease	Ionis			
IONIS-$C9_{Rx}$	C9-ALS	Biogen			
IONIS-$MAPT_{Rx}$	Alzheimer's disease	Biogen			
ION859 (LRRK2)	Parkinson's disease	Biogen			
ION464 (SNCA)	MSA & Parkinson's disease	Biogen			
ION541 (ATXN2)	ALS	Biogen			
ION582 (UBE3A)	Angelman syndrome	Biogen			
Tominersen	HTT	Roche			
IONIS-DNM2-2.5_{Rx}	Centronuclear myopathy	Dynacure			
SPECIALTY RARE					
Sapablursen	β-thalassemia	Ionis			
Sapablursen	Polycythemia vera	Ionis			
Cimdelirsen (GHR)	Acromegaly	Ionis			
OTHER MEDICINES					
ION224 (DGAT2)	NASH	Ionis			
Bepirovirsen	Hepatitis B virus infection	GSK			
IONIS-FB-L_{Rx}	IgA Nephropathy	Roche			
IONIS-FB-L_{Rx}	Geographic atrophy/AMD	Roche			
ION357 (RHO)	Autosomal dominant retinitis pigmentosa	ProQR			
IONIS-$GCGR_{Rx}$	Diabetes	Suzhou-Ribo*			
ION736 (FOXP3)	Cancer	AstraZeneca			
IONIS-AR-2.5_{Rx}	Prostate cancer	Flamingo/ Suzhou-Ribo*			
Danvatirsen (STAT3)	Cancer	Flamingo			

*China Only

Our Phase 3 Medicines

We currently have six medicines in Phase 3 studies for eight indications: eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen.



Eplontersen (TTR) – Eplontersen (formerly IONIS-TTR-L_{Rx}) is an investigational LICA medicine we designed to inhibit the production of TTR protein. We are developing eplontersen as a monthly self-administered subcutaneous injection to treat all types of ATTR. ATTR amyloidosis is a systemic, progressive and fatal disease in which patients experience multiple overlapping clinical manifestations caused by the inappropriate formation and aggregation of TTR amyloid deposits in various tissues and organs, including peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to organ failure and eventually death.

Polyneuropathy due to hATTR is caused by the accumulation of misfolded mutated TTR protein in the peripheral nerves. Patients with polyneuropathy due to hATTR experience ongoing debilitating nerve damage throughout their body resulting in the progressive loss of motor functions, such as walking. These patients also accumulate TTR in other major organs, which progressively compromises their function and eventually leads to death within five to fifteen years of disease onset. There are an estimated 40,000 patients with polyneuropathy due to hATTR worldwide.

ATTR cardiomyopathy is caused by the accumulation of misfolded TTR protein in the cardiac muscle. Patients experience ongoing debilitating heart damage resulting in progressive heart failure, which results in death within 3 to 5 years from disease onset. ATTR cardiomyopathy includes both the genetic and wild-type form of the disease. There are an estimated 300,000 to 500,000 patients with ATTR cardiomyopathy worldwide.

Often patients with the polyneuropathy form of TTR amyloidosis will have TTR build up in the heart and experience cardiomyopathy symptoms. Similarly, patients with the cardiomyopathy form of TTR amyloidosis may often have TTR build up in their peripheral nerves and experience nerve damage and progressive difficulty with motor functions.

In November 2019, we initiated the NEURO-TTRansform Phase 3 study of eplontersen in patients with polyneuropathy caused by hATTR amyloidosis. NEURO-TTRansform is a global, multi-center, randomized, open-label study designed to evaluate the efficacy, safety and tolerability of eplontersen. The NEURO-TTRansform study is fully enrolled with 168 patients. We expect data from the NEURO-TTRansform study in mid-2022. The current study will be compared to the historical placebo arm from the TEGSEDI (inotersen) NEURO-TTR Phase 3 study. The NEURO-TTRansform study includes multiple primary endpoints, including the percent change from baseline in serum TTR concentration modified Neuropathy Impairment Score +7, or mNIS+7, a measure of neuropathic disease progression and in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy, or Norfolk QoL-DN.

In January 2020, we initiated the CARDIO-TTRansform Phase 3 cardiovascular outcome study of eplontersen in patients with ATTR cardiomyopathy. CARDIO-TTRansform is a global, multi-center, randomized, double-blind, placebo-controlled study in up to 750 patients designed to evaluate the efficacy, safety and tolerability of eplontersen. The CARDIO-TTRansform study includes co-primary outcome measures of cardiovascular death and frequency of cardiovascular clinical events.

In September 2019, we reported results from the Phase 1 study with eplontersen in healthy volunteers at the Heart Failure Society of America Annual Meeting. In this study, subjects treated with eplontersen achieved dose-dependent reductions of TTR protein of up to 94 percent and eplontersen had a favorable safety and tolerability profile supportive of continued development.

In January 2022, the FDA granted an Orphan Medicine Designation for eplontersen.

In December 2021, we entered into an agreement with AstraZeneca to jointly develop and commercialize eplontersen in the U.S. AstraZeneca obtained exclusive rights to commercialize eplontersen outside the U.S, except for certain Latin American countries.

Olezarsen (ApoC-III) – Olezarsen (formerly IONIS-APOCIII-L_{Rx}) is an investigational LICA medicine we designed to inhibit the production of apoC-III for patients who are at risk of disease due to elevated triglyceride levels. ApoC-III is a protein produced in the liver that regulates triglyceride metabolism in the blood. People with severely elevated triglycerides, such as people with FCS, are at high risk for acute pancreatitis and an increased risk of CVD. It is estimated that there are between 3,000 to 5,000 patients with FCS worldwide and more than three million patients with severely high triglycerides in the U.S.

In December 2020, we initiated our first Phase 3 study of olezarsen, BALANCE, in patients with FCS. BALANCE is a global, multi-center, randomized, double-blind, placebo-controlled study enrolling up to 60 patients (age 18 and over) designed to assess the efficacy, safety and tolerability of olezarsen. The primary endpoint is percent change from baseline in fasting triglyceride levels at six months compared to placebo.

In November 2021, we initiated a second Phase 3 study of olezarsen, CORE, in patients with SHTG. CORE is a global, multi-center, randomized, double-blind, placebo-controlled study enrolling up to 450 patients designed to assess the efficacy, safety and tolerability of olezarsen. The CORE study will compare olezarsen to placebo in patients with triglyceride levels equal to or greater than 500 mg/dL who are on currently available therapies for elevated triglycerides. The primary endpoint of the study is the percent change in fasting triglycerides from baseline at month 6.

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

Donidalorsen (PKK) – Donidalorsen (formerly IONIS-PKK-L_{Rx}) is an investigational LICA medicine we designed to inhibit the production of prekallikrein, or PKK, to treat people with HAE. HAE is a rare genetic disease that is characterized by rapid and painful attacks of inflammation in the hands, feet, limbs, face, abdomen, larynx, and trachea and can be fatal if swelling occurs in the larynx. PKK plays an important role in the activation of inflammatory mediators associated with acute attacks of HAE. By inhibiting the production of PKK, donidalorsen could be an effective prophylactic approach to preventing or reducing the severity of HAE attacks. It is estimated that there are more than 20,000 patients with HAE in the U.S. and EU.

In November 2021, we initiated the Phase 3 study of donidalorsen, OASIS-HAE, in patients with HAE. OASIS-HAE is a multi-center, randomized, double-blind placebo-controlled study in up to 84 patients designed to assess the efficacy, safety and tolerability of olezarsen. The primary endpoint is the time-normalized number of investigator-confirmed HAE attacks per month from Week 1 to Week 25.

In March 2021, we reported positive results from a Phase 2 clinical study of donidalorsen in patients with HAE. Patients received either donidalorsen 80mg or placebo subcutaneously once monthly for 17 weeks. The Phase 2 study met its primary and secondary endpoints, achieving significant reductions in the number of attacks suffered by patients with HAE compared to placebo. The study demonstrated a mean reduction of 90 percent in the number of monthly HAE attacks in weeks one to 17 of the study ($p < 0.001$) and a mean reduction of 97 percent in the number of monthly HAE attacks in weeks five to 17 ($p = 0.003$). In weeks five to 17, 92 percent of patients treated with donidalorsen were attack-free compared to 0 percent in the placebo group ($p < 0.001$). Additionally, in November 2021 we reported additional data from the Phase 2 study, including that donidalorsen demonstrated an overall reduction in moderate to severe attacks starting with the second dose. For the final month of the study, all donidalorsen treated patients were attack-free. Donidalorsen had a favorable safety and tolerability profile supportive of continued development.

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

ION363 (FUS) – ION363 is an investigational antisense medicine we designed to reduce the production of the FUS protein to treat people with ALS caused by mutations in the FUS gene. Because antisense-mediated reduction of mutant FUS protein in a FUS-ALS mouse model demonstrated the ability to prevent motor neuron loss, it is hypothesized that reduction of FUS protein will reverse or prevent disease progression in FUS-ALS patients. It is estimated that there are approximately 350 patients with FUS-ALS in G7 countries (comprised of Canada, France, Germany, Italy, Japan, the United Kingdom and the U.S.).

In April 2021, we initiated a Phase 3 study of ION363 in patients with FUS-ALS. The Phase 3 trial of ION363 is a global, multi-center, randomized, double-blind, placebo-controlled study enrolling up to 64 patients designed to assess the efficacy, safety and tolerability of ION363. Part 1 of the trial will consist of patients randomized to receive a multi-dose regimen of ION363 or placebo for 29 weeks, followed by Part 2, which will be an open-label period in which all patients in the trial will receive ION363 for 73 weeks. The primary endpoint is change from baseline as measured by the ALSFRS-R Total Score, time of rescue or discontinuation from Part 1 and entering Part 2 due to a deterioration in function, and Ventilation Assistance-free survival, or VAFS.

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

In December 2019, Novartis initiated the Phase 3 study of pelacarsen, Lp(a) HORIZON, in patients with elevated Lp(a) levels and a prior cardiovascular event. Lp(a) HORIZON is a global, multi-center, randomized, double-blind, placebo-controlled cardiovascular outcomes study in more than 8,000 patients designed to assess the efficacy, safety and tolerability of pelacarsen. Patients will be treated with 80 mg of pelacarsen administered monthly by subcutaneous injection. The primary endpoint in Lp(a) HORIZON is the time to occurrence of first major adverse cardiovascular event, or MACE. In August 2021, we announced that the Lp(a) HORIZON study had reached 50 percent enrollment.

In November 2018, we reported results of the Phase 2 study of pelacarsen in patients with hyperlipoproteinemia(a) at the American Heart Association, or AHA, annual meeting. In the Phase 2 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. Pelacarsen had a favorable safety and tolerability profile supportive of continued development.

In February 2019, Novartis exercised its option to license pelacarsen. As a result, Novartis is responsible for global development, regulatory and commercialization activities, and costs for pelacarsen.

Tofersen (SOD1) (BIIB067) **–** Tofersen (formerly IONIS-$SOD1_{Rx}$) is an investigational antisense medicine we designed to inhibit the production of superoxide dismutase 1, or SOD1, which is a well understood genetic cause of ALS. SOD1-ALS is a rare, fatal, neurodegenerative disorder caused by a mutation in the *SOD1* gene leading to a progressive loss of motor neurons. As a result, people with SOD1-ALS experience increasing muscle weakness, loss of movement, difficulty breathing and swallowing and eventually succumb to the disease. Current treatment options for people with SOD1-ALS are extremely limited, with no medicines that significantly slow disease progression. Tofersen is one of four medicines we have in development to treat ALS. It is estimated that there are approximately 1,400 patients with SOD1-ALS in G7 countries.

In October 2021, Biogen announced topline results of the Phase 3 VALOR study of tofersen in patients with SOD1-ALS designed to assess the efficacy, safety and tolerability of tofersen. While tofersen did not meet the primary endpoint of change from baseline to 28 weeks in the ALSFRS-R, trends favoring tofersen were seen across multiple secondary and exploratory measures of disease activity and clinical function. As a result, Biogen is actively engaged with regulators to determine next steps for the program. Additionally, in October 2021, Biogen announced that it would expand eligibility for its ongoing EAP to all people with SOD1-ALS, where permitted.

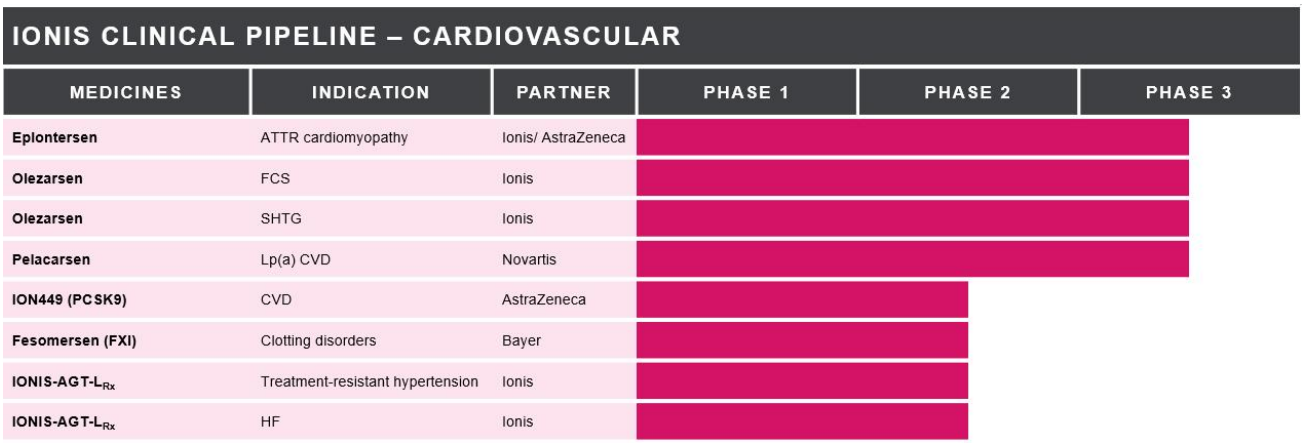
In April 2021, Biogen initiated a second Phase 3 study of tofersen, ATLAS, in presymptomatic individuals with a SOD1 genetic mutation and biomarker evidence of disease activity. ATLAS is a multi-center, randomized, double-blind, placebo-controlled study enrolling up to 150 subjects designed to assess the efficacy, safety and tolerability of tofersen in presymptomatic individuals with a SOD1 genetic mutation and biomarker evidence of disease activity.

Biogen conducted a Phase 1/2 study that demonstrated proof of biology and proof of concept. At the highest dose tested, treatment with tofersen over a three month period resulted in a statistically significant lowering of SOD1 protein levels in the cerebrospinal fluid, or CSF, and positive numerical trends across three efficacy endpoints compared to placebo, including slowing of clinical decline as measured by the ALSFRS-R. Tofersen had a favorable safety and tolerability profile supportive of continued development.

In December 2018, Biogen exercised its option to license tofersen, as a result, Biogen is responsible for global development, regulatory and commercialization activities, and costs for tofersen.

Our Cardiovascular Medicines in Development

According to the World Health Organization, or WHO, CVD remains the number one cause of death globally. An estimated 17.9 million people died from CVD in 2019, representing approximately 30 percent of all deaths globally. Our cardiovascular medicines target the major risk factors of cardiovascular disease, including cholesterol, triglycerides, and hypertension.



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

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

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

ION449 (PCSK9) (AZD8233) – ION449 (formerly IONIS-AZ4-2.5-L_{-Rx}) is an investigational LICA medicine we designed to reduce the production of proprotein convertase subtilisin/kexin type 9, or PCSK9, in the liver. PCSK9 is integrally involved in the regulation of LDL-cholesterol. Genetic studies have shown that individuals with life-long reductions of LDL-C due to reduced function of PCSK9 have substantially reduced risk of CVD.

In November 2020, AstraZeneca initiated the Phase 2b study of ION449 in patients with LDL-C levels between 70 and 190 mg/dl and receiving statin therapy. The study is a randomized, double-blind, placebo-controlled clinical study in approximately 110 patients to assess the efficacy, safety and tolerability of ION449. The primary objective is to assess the effect of different doses of ION449 on LDL-C compared to placebo at Week 12 in patients taking baseline statin therapy. The study will evaluate three dose levels of ION449 versus placebo, all administered once a month by subcutaneous injection.

In November 2021, we reported positive results from the Phase 1 study of ION449 in patients with dyslipidemia. Participants were treated with multiple ascending subcutaneous doses and ION449 demonstrated dose-dependent mean reductions in circulating plasma PCSK9 and LDL-C levels and had a favorable safety and tolerability profile supportive of continued development.

In October 2020, we reported positive results from the Phase 1 study of ION449 in healthy volunteers. Participants were treated with a single subcutaneous dose and ION449 demonstrated dose-dependent mean reductions in circulating plasma PCSK9 and LDL-C levels and had a favorable safety and tolerability profile supportive of continued development.

We licensed ION449 to AstraZeneca under our cardiovascular, renal and metabolic diseases collaboration. As a result, AstraZeneca is responsible for global development, regulatory and commercialization activities, and costs for ION449.

Fesomersen (FXI) (BAY2976217) – Fesomersen (formerly IONIS-FXI-L_{Rx}) is an investigational LICA medicine we designed to inhibit the production of Factor XI. Factor XI is a clotting factor produced in the liver that is important in the growth of blood clots. Thrombosis, characterized by the formation of a blood clot inside blood vessels, can cause heart attacks and strokes. People who are deficient in Factor XI have a lower incidence of thromboembolic events with minimal increase in bleeding risk. Although currently available anticoagulants reduce the risk of thrombosis, physicians associate these anticoagulants with increased bleeding, which can be fatal. By inhibiting Factor XI production, we believe that fesomersen can be used broadly as an anti-thrombotic in many different therapeutic settings for which additional safe and well tolerated anti-thrombotic medicines are needed.

In August 2020, Bayer initiated the RE-THINc Phase 2b study of fesomersen in patients with end-stage renal disease, or ESRD, on hemodialysis. RE-THINc is a randomized, blinded, placebo-controlled study in approximately 290 patients to assess the efficacy, safety and tolerability of fesomersen. The study is designed to evaluate multiple monthly doses administered subcutaneously. The primary endpoint is incidence of major bleeding and clinically relevant non-major bleeding.

We conducted a Phase 1, blinded, randomized, placebo-controlled, dose-escalation study of fesomersen in healthy volunteers. In this study, fesomersen produced significant reductions in FXI activity and FXI antigen, without evidence of increased bleeding and had a favorable safety and tolerability profile supportive of continued development.

In February 2017, we licensed fesomersen to Bayer. As a result, Bayer is responsible for global development, regulatory and commercialization activities, and costs for fesomersen.

IONIS-AGT-L_{Rx} – IONIS-AGT-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of angiotensinogen to decrease blood pressure in people with treatment resistant hypertension, or TRH. Despite the availability of antihypertensive agents, TRH is still a major contributor to cardiovascular and renal disease. Approximately 140 million adults globally and approximately 10 million adults in the U.S. have resistant hypertension, defined as failure to achieve a blood pressure goal of 140/90 (systolic/diastolic) despite the use of three or more antihypertensive medications. People with TRH have been found to have a three-fold higher chance of having fatal and non-fatal cardiovascular events relative to those with controlled hypertension.

We are also studying IONIS-AGT-L_{Rx} in patients with chronic heart failure with reduced ejection fraction. Heart failure, or HF, afflicts approximately 6.5 million patients in the United States, or U.S., and 26 million worldwide. As the population ages, HF incidence is increasing, and more than 550,000 patients are diagnosed with HF each year. HF is responsible for more hospitalizations than all forms of cancer combined and is the most common diagnosis in hospital patients 65 years and older. Every year over 1 million patients are hospitalized for HF in the U.S. and Europe, accounting for 6.5 million hospital days. High rates of hospitalizations with frequent readmission (almost 25 percent of patients with HF are readmitted within 30 days) along with other direct and indirect costs, also place an enormous economic burden on healthcare systems. Despite new advances in medical therapy, the residual risk for patients with HF is still high.

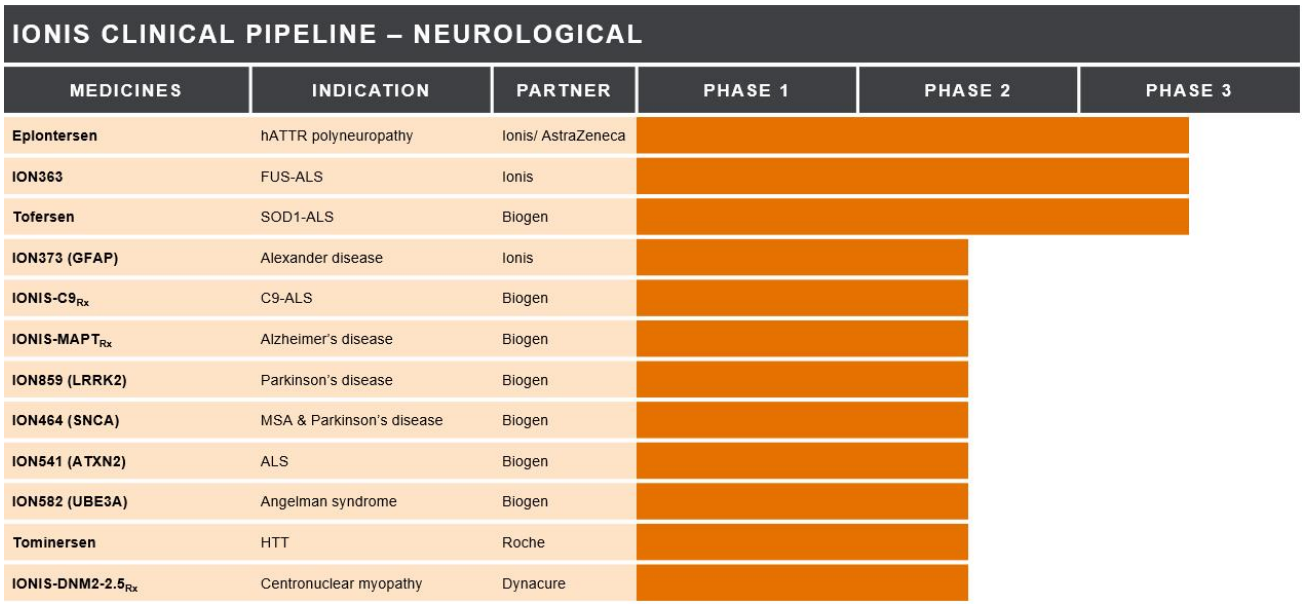
In January 2021, we initiated a Phase 2b clinical study of IONIS-AGT-L_{Rx} in patients with hypertension uncontrolled with three or more antihypertensive medications, including angiotensin-converting enzyme, or ACE, inhibitors or angiotensin II receptor blockers, or ARBs. The study is a randomized, double-blinded, placebo-controlled study in approximately 150 patients to assess the efficacy, safety and tolerability of IONIS-AGT-L_{Rx}. We designed the study to evaluate multiple doses administered subcutaneously. The primary endpoint is the change in systolic blood pressure, or SBP, from baseline.

In September 2021, we initiated a Phase 2 clinical study of IONIS-AGT-L_{Rx} in patients with chronic HF with reduced ejection fraction. The study is a randomized, double-blind, placebo-controlled study in approximately 75 patients to assess the safety, tolerability, and efficacy of IONIS-AGT-L_{Rx}. We designed the study to evaluate multiple doses administered subcutaneously. The primary endpoint is the percent change in plasma AGT concentration from baseline.

We evaluated IONIS-AGT-L_{Rx} in two randomized, double-blinded, placebo-controlled Phase 2 studies. The first study was in people with mild hypertension and the second was in people with TRH who were on two or three antihypertensive medications, including ACE inhibitors or ARBs. IONIS-AGT-L_{Rx} significantly reduced AGT levels compared with placebo in both studies. Although not powered for this endpoint, trends were noted in blood pressure reduction and IONIS-AGT-L_{Rx} had a favorable safety and tolerability profile supportive of continued development.

Our Neurological Medicines in Development

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



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

ION363 – See the medicine description under "Our Phase 3 Medicines" section above.

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

ION373 (GFAP) – ION373 is an investigational antisense medicine targeting glial fibrillary acidic protein, or GFAP, mRNA we designed to inhibit the production of GFAP. We are developing ION373 as a potential therapy for Alexander disease, or AxD. AxD is a rare progressive and fatal neurological disease that affects the myelin sheath which protects nerve fibers. AxD is caused by a gain-of-function mutation in the GFAP gene and is characterized by progressive deterioration, including loss of skills and independence, generally leading to death in childhood or early adulthood.

Two major types of AxD have been defined. Type I onset typically occurs before 4 years of age and patients can experience head enlargement, seizures, limb stiffness, delayed or declining cognition, and lack of growth. Type II onset typically occurs after the age of 4 and symptoms can include difficulty speaking, swallowing, and making coordinated movements. AxD is most often fatal. There are treatments that can relieve symptoms, but there is no disease modifying therapy yet available to patients.

In April 2021, we initiated a pivotal study of ION373 in patients with AxD. The Phase 2/3 study of ION373 is a multi-center, double-blind, placebo-controlled, multiple-ascending dose study in up to 58 patients with AxD designed to assess the efficacy, safety and tolerability of ION373. Patients will receive ION373 or placebo for a 60-week period, after which all patients in the study will receive ION373 for a 60-week open-label treatment period. The primary endpoint is the change from baseline in the 10-Meter Walk Test, or 10MWT.

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

In August 2018, Biogen initiated a Phase 1/2 clinical study of IONIS-C9$_{Rx}$ in adult patients with C9-ALS. The Phase 1/2 study is a global, multi-center, randomized, double-blinded, placebo-controlled study designed to assess safety, tolerability and activity of multiple ascending doses of IONIS-C9$_{Rx}$ administered intrathecally.

IONIS-C9$_{Rx}$ is being developed under our 2013 Strategic Neurology collaboration with Biogen.

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

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

In July 2021, we and Biogen reported positive topline data from our Phase 1/2 study of IONIS-MAPT$_{Rx}$ in patients with mild Alzheimer's disease at the Alzheimer's Association International Conference, or AAIC. The Phase 1/2 study was a blinded, randomized, placebo-controlled, dose-escalation of IONIS-MAPT$_{Rx}$ to evaluate the safety and activity of once-monthly intrathecal injections of IONIS-MAPT$_{Rx}$ in patients with mild AD. The study showed that IONIS-MAPT$_{Rx}$ met its primary objective of safety and tolerability in patients with mild Alzheimer's disease. The study demonstrated robust time and dose dependent lowering of tau protein in cerebrospinal fluid over the three-month treatment period and sustained reductions during the six-month post-treatment period and IONIS-MAPT$_{Rx}$ had a favorable safety and tolerability profile supportive of continued development.

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

ION859 (LRRK2) (BIIB094) – ION859 is an investigational antisense medicine we designed to inhibit the production of the Leucine Rich Repeat Kinase 2, or LRRK2, protein as a potential therapy for Parkinson's disease, or PD. The most common genetic mutations in PD are found in the LRRK2 protein. It is believed that increased LRRK2 protein activity could be one of the key drivers for developing PD. PD is a progressive neurodegenerative disease characterized by loss of neurons in the motor system. Patients with PD can experience tremors, loss of balance and coordination, stiffness, slowing of movement, changes in speech and in some cases cognitive decline. PD is ultimately fatal. There are treatments that can relieve symptoms, but there is no disease modifying therapy.

In August 2019, Biogen initiated a Phase 1/2 study evaluating ION859 in adult patients with PD. The Phase 1/2 study is a global, multi-center, randomized, double-blinded, placebo-controlled study designed to assess the safety, tolerability and activity of multiple ascending doses of ION859 administered intrathecally.

ION859 is being developed under our 2013 Strategic Neurology collaboration with Biogen.

ION464 (SNCA) (BIIB101) – ION464 is an investigational antisense medicine we designed to inhibit the production of the alpha-synuclein protein as a potential therapy for PD, Multiple System Atrophy, or MSA, and related synucleinopathies. Alpha-synuclein protein abnormally accumulates in the brains of PD and MSA patients and is thought to be one of the key drivers of these diseases. It is believed that decreasing the production of the alpha-synuclein protein will reduce the toxic effects of gain-of-function mutations.

In July 2020, we initiated a Phase 1/2 study evaluating ION464 in patients with MSA. The current study is a multi-center, randomized, double-blinded, placebo-controlled study designed to assess the safety and tolerability of multiple doses of ION464 administered intrathecally.

ION464 is being developed under our 2013 Strategic Neurology collaboration with Biogen.

ION541 (ATXN2) (BIIB105) – ION541 is an investigational antisense medicine we designed to reduce the production of the ataxin-2, or ATXN2, protein for the potential treatment of ALS. The reduction of ATXN2 has been shown to decrease aggregation of TDP-43, a toxic RNA binding protein found in most patients with ALS, including the approximately 90 percent of the ALS population with no known family history of ALS. ION541 is one of four medicines we have in development to treat ALS.

In October 2020, Biogen initiated a Phase 1/2 clinical study evaluating ION541 in this broad ALS population. The current study is a randomized, blinded, placebo-controlled study designed to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of ION541 administered intrathecally.

ION541 is being developed under our 2013 Strategic Neurology collaboration with Biogen.

ION582 (UBE3A) (BIIB121) – ION582 is an investigational antisense medicine we designed to inhibit the expression of the UBE3A transcript, or UBE3A-ATS for the potential treatment of Angelman Syndrome, or AS. AS is a rare, genetic neurological disease caused by the loss of function of the maternally inherited *UBE3A* gene. Angelman syndrome typically presents in infancy and is characterized by intellectual disability, balance issues, motor impairment, and debilitating seizures. Some patients are unable to walk or speak. Some symptoms can be managed with existing drugs; however, there is no disease modifying therapy. It is estimated that there are more than 60,000 patients with AS in the U.S. and EU.

In December 2021, we initiated the Phase 1/2 study, HALOS, of ION582 in patients with Angelman syndrome. The study is an open label dose-escalation study enrolling up to 44 participants to assess the safety, tolerability and activity of multiple ascending doses of ION582.

ION582 is being developed under our 2012 Neurology collaboration with Biogen.

Tominersen (HTT) (RG6042**) –** Tominersen (formerly IONIS-HTT_{Rx}) is an investigational antisense medicine we designed to target the underlying cause of Huntington's disease, or HD, by reducing the production of all forms of the huntingtin protein, or HTT, including its mutated variant, or mHTT. HD is an inherited genetic brain disorder that results in the progressive loss of both mental faculties and physical control. It is caused by the expansion of the CAG trinucleotide sequence in the HTT gene. The resulting mutant HTT protein is toxic and gradually destroys neurons. Symptoms usually appear between the ages of 30 and 50 and worsen over a 10 to 25-year period. Ultimately, the weakened individual succumbs to pneumonia, heart failure or other complications. Presently, there is no effective treatment or cure for the disease, and currently available medicines only mask the patient's symptoms but do not slow down the underlying loss of neurons.

In January 2022, Roche announced plans to initiate a new Phase 2 trial to evaluate tominersen in patients with HD based on findings from a post-hoc analysis of the Phase 3 GENERATION HD1 study. The findings from the post-hoc analysis suggested tominersen may benefit younger adult patients with lower disease burden. As a result, Roche is in the early stages of designing a Phase 2 clinical trial to explore different doses of tominersen in this patient population.

Roche conducted the Phase 3 study, GENERATION HD1,of tominersen in patients with HD. The Phase 3 study was a randomized, multicenter, double-blind, placebo-controlled study that recruited 791 participants from 18 countries around the world. In March 2021, Roche announced that dosing would be stopped in the study following a recommendation from the independent data monitoring committee, or iDMC, based on an overall benefit/risk assessment. The study is ongoing without dosing to allow participants to be followed for safety and clinical outcomes. Roche anticipates the study will complete in March/April 2022.

Roche is also conducting the GEN-EXTEND study, an OLE study for participants coming from any prior Roche HD study. The study is ongoing without dosing to allow participants to be followed for safety and clinical outcomes. Roche anticipates the study will complete in March/April 2022. In parallel with the OLE, Roche initiated a natural history study in a similar patient population to the OLE aimed at further understanding the natural progression of HD.

We completed a randomized, placebo-controlled, dose escalation, Phase 1/2 clinical study of tominersen in patients with early-stage HD. In this study, we observed dose-dependent reductions of mHTT among patients treated with tominersen and a favorable safety and tolerability profile supporting continued development. The data from this study were published in *The New England Journal of Medicine* in May 2019.

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

In December 2017, Roche exercised its option to license tominersen. As a result, Roche is responsible for global development, regulatory and commercialization activities, and costs for tominersen.

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

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

In the fourth quarter of 2017, we licensed IONIS-DNM2-2.5$_{Rx}$ to Dynacure. As a result, Dynacure is responsible for global development, regulatory and commercialization activities, and costs for IONIS-DNM2-2.5$_{Rx}$.

Specialty Rare Medicines in Development

Our emerging specialty rare disease pipeline is comprised of medicines that are outside of our cardiovascular and neurological franchises, but we believe could represent a compelling opportunity for us.

IONIS CLINICAL PIPELINE – SPECIALTY RARE

MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
Donidalorsen	HAE	Ionis			
Sapablursen	β-thalassemia	Ionis			
Sapablursen	Polycythemia vera	Ionis			
Cimdelirsen (GHR)	Acromegaly	Ionis			

Sapablursen (TMPRSS6) – Sapablursen (formerly IONIS-TMPRSS6-L$_{Rx}$) is an investigational LICA medicine we designed to target the TMPRSS6 gene to modulate the production of hepcidin, which is the key regulator of iron homeostasis. By modulating hepcidin expression, sapablursen has the potential to positively impact diseases characterized by iron excess, such as β-thalassemia, and iron deficiency, such as polycythemia vera, or PV.

β-thalassemia is a rare, genetic and potentially fatal form of chronic anemia resulting in hepcidin deficiency, severely reduced red blood cell production and iron toxicity. In some cases, iron accumulates in major organs, such as the heart and liver, which can be fatal. The current standard-of-care involves symptom management, including blood transfusions and iron chelation. There are no approved disease-modifying treatments for β-thalassemia.

PV is a rare, non-genetic and potentially fatal disease caused by overproduction of red blood cells. This overproduction leads to a thickening of the blood, which increases patients' risk of life-threatening blood clots, including in the lungs, heart and brain. Patients with PV also experience severe iron deficiency due to hepcidin overexpression. The current standard-of-care for PV involves symptom management. There are no approved disease-modifying treatments for PV.

In August 2020, we initiated a Phase 2 study evaluating sapablursen in patients with non-transfusion dependent, or NTDT, β-thalassemia intermedia. The Phase 2 study is multi-center, randomized, open-label study in approximately 36 patients we designed assess the efficacy, safety, and tolerability of sapablursen administered monthly subcutaneously. The primary endpoint is the percentage of participants with a greater than or equal to 1.0 g/dl increase from baseline in hemoglobin at week 27.

In January 2022 we initiated a Phase 2 study evaluating sapablursen in patients with Phlebotomy Dependent Polycythemia Vera, or PD-PV. The Phase 2 study is a multi-center, randomized, open-label study in approximately 40 patients designed to assess the efficacy, safety and tolerability of sapablursen. The primary endpoint is Change in the frequency of phlebotomy comparing baseline with the last 20 weeks of the 37-week treatment period.

In December 2018, we presented positive data from our Phase 1 study of sapablursen in healthy volunteers at the American Society of Hematology Annual Meeting. The Phase 1 study demonstrated dose-dependent reductions of serum iron and serum transferrin saturation with sapablursen. Additionally, we observed an increase in serum hepcidin and predicted changes in hemoglobin and sapablursen had a favorable safety and tolerability profile supportive of continued development.

Cimdelirsen (GHR) – Cimdelirsen (formerly IONIS-GHR-L_{Rx}) is an investigational LICA medicine we designed to inhibit the production of growth hormone receptor, or GHr, to decrease the circulating level of insulin-like growth factor-1, or IGF-1. Elevated levels of IGF-1 results in acromegaly, a chronic, slowly progressing and potentially fatal disease. Patients with acromegaly experience multiple chronic conditions, such as type 2 diabetes, hypertension, and respiratory complications and premature death. Current treatments to block IGF-1 are often unsuccessful. Drug treatments to normalize IGF-1 levels are also available but are associated with potentially serious side effects.

In January 2021, we initiated a Phase 2 study of cimdelirsen evaluating cimdelirsen as a monotherapy in patients with acromegaly. The Phase 2 study is a multi-center, randomized, open label study in approximately 40 patients to assess the efficacy, safety and tolerability of cimdelirsen. The primary endpoint is the percent change from baseline in IGF-1 to week 27.

We completed a Phase 2 study evaluating cimdelirsen as an add-on therapy in patients with uncontrolled acromegaly despite stable therapy with long-acting somatostatin receptor ligands, or SRL. Based on the results of this Phase 2 study and a preliminary analysis of the ongoing open-label study, proof of mechanism was achieved with a strong indication of proof of concept supporting the continued development of cimdelirsen. Due to enrollment difficulties associated with the COVID-19 pandemic, the study closed early, resulting in smaller cohort sizes than planned. While no longer powered to assess the primary endpoint (percentage of IGF- lowering at Day 141) in accordance with the protocol, the study did permit placebo-controlled evaluation of safety and efficacy. Cimdelirsen had a favorable safety and tolerability profile supportive of continued development.

We also completed a Phase 1, blinded, placebo-controlled, dose-escalation study of cimdelirsen in healthy volunteers. In this study, cimdelirsen demonstrated a favorable safety and tolerability profile supporting continued development.

Other Medicines in Development

We continue to advance other medicines in clinical development targeting metabolic diseases, infectious diseases, renal diseases, ophthalmic diseases and cancer.

IONIS CLINICAL PIPELINE- OTHER MEDICINES

MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
ION224 (DGAT2)	NASH	Ionis			
Bepirovirsen	Hepatitis B virus infection	GSK			
IONIS-FB-L_{Rx}	IgA Nephropathy	Roche			
IONIS-FB-L_{Rx}	Geographic atrophy/AMD	Roche			
IONIS-GCGR$_{Rx}$	Diabetes	Suzhou-Ribo*			
ION357 (RHO)	Autosomal dominant retinitis pigmentosa	ProQR			
ION736 (FOXP3)	Cancer	AstraZeneca			
IONIS-AR-2.5$_{Rx}$	Prostate cancer	Flamingo/ Suzhou-Ribo*			
Danvatirsen (STAT3)	Cancer	Flamingo			

*China Only

ION224 (DGAT) – ION224 is an investigational LICA medicine designed to reduce the production of DGAT2, or diacylglycerol acyltransferase 2, to treat patients with nonalcoholic steatohepatitis, or NASH. NASH is a common liver disease characterized by liver steatosis, inflammation and scarring and can lead to increased risk of cardiovascular disease, liver cancer, need for liver transplantation and early death. 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 studies, antisense inhibition of DGAT2 significantly improved liver steatosis, lowered blood lipid levels and reversed diet-induced insulin resistance.

NASH is sometimes considered a “silent” liver disease because people with early-stage NASH feel well, even though they are starting to accumulate fat in their livers and may not be aware that they have the disease. However, NASH can develop into more severe diseases such as liver cirrhosis and liver failure. Currently, liver transplant is the only therapeutic option for patients with liver cirrhosis. In addition, NASH has been shown to be a major risk factor for the development of liver cancer.

Nonalcoholic fatty liver disease, or NAFLD, describes the full spectrum of liver disease progression from fatty liver to NASH to cirrhosis to hepatocellular carcinoma. NASH epidemiology studies have estimated 13 to 32 percent of the global population has NAFLD, 1.5 to 6.5 percent have NASH, and approximately 9 percent of NASH patients progress to advanced liver disease. There are currently no commercially available medications to treat NASH.

In June 2021, we initiated a Phase 2 study of ION224 in patients with confirmed non-alcoholic steatohepatitis. The Phase 2 study is a multi-center, randomized, double-blind, placebo-controlled clinical study enrolling approximately 150 patients designed to assess the efficacy, safety and tolerability of multiple subcutaneous doses of ION224 on NASH histologic improvement.

Bepirovirsen (HBV) (GSK3228836) **–** Bepirovirsen (formerly IONIS-HBV_{Rx}) is an investigational antisense medicine we designed to inhibit the production of viral proteins associated with hepatitis B virus, or HBV. These include proteins associated with infection and replication, including the hepatitis B surface antigen, or HBsAg, which is present in both acute and chronic infections and is associated with a poor prognosis in people with chronic HBV infection.

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

GSK is conducting a broad Phase 2 program for bepirovirsen. The B-Clear study is a Phase 2b randomized, double-blinded, placebo-controlled study in approximately 440 patients with chronic HBV. The primary endpoint is the percentage of patients achieving HBV surface antigen and HBV DNA less than the lower limit of quantitation. Additionally, GSK is conducting two open label Phase 2 studies and a long-term follow up study in patients with chronic HBV.

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

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

IONIS-FB-L_{Rx} – IONIS-FB-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of complement factor B, or FB. Genetic association studies have shown that overaction of this cascade has been associated with the development of several complement-mediated diseases, including IgA nephropathy, or IgAN, and dry age-related macular degeneration, or AMD.

IgAN is one of the most common causes of inflammation that impairs the filtering ability of kidneys and is an important cause of chronic kidney disease and renal failure. Also known as Berger’s disease, IgAN is characterized by deposits of IgA in the kidneys, resulting in inflammation and tissue damage.

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

In September 2019, we initiated a Phase 2 study of IONIS-FB-L_{Rx} in patients with IgA nephropathy. The Phase 2 study is a single-arm, open-label study designed to assess the efficacy, safety and tolerability of IONIS-FB-L_{Rx} administered subcutaneously in adults with primary IgA nephropathy. The primary endpoint is the percent reduction in 24-hour urine protein excretion from baseline to week 29.

In May 2017, we reported data from a Phase 1 study evaluating IONIS-FB-L_{Rx} in 54 healthy volunteers. The Phase 1 study was a randomized, placebo-controlled, dose-escalation study. Subjects were 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. IONIS-FB-L_{Rx} had a favorable safety and tolerability profile supportive of continued development.

In June 2019, we initiated a Phase 2 study evaluating IONIS-FB-L_{Rx} in patients with GA secondary to age-related macular degeneration. The study is a randomized, masked, placebo-controlled study designed to assess the efficacy, safety and tolerability of multiple ascending doses of IONIS-FB-L_{Rx} administered subcutaneously in adults with GA. The primary endpoint is the absolute change from baseline in GA area at week 49.

IONIS-FB-L_{Rx} is being developed under our collaboration with Roche.

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

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

In October 2019, Suzhou-Ribo initiated a Phase 2 clinical study evaluating IONIS-GCGR$_{Rx}$ in patients with type 2 diabetes.

ION357 (RHO) (QR-1123) **–** ION357 (formerly IONIS-RHO-2.5$_{Rx}$), is an investigational antisense medicine we designed to treat patients with a genetic form of autosomal dominant retinitis pigmentosa by inhibiting the production of the rhodopsin P23H mutant protein in the eye while allowing normal protein to be expressed.

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

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

In the fourth quarter of 2018, we licensed ION357 to ProQR. As a result, ProQR is responsible for global development, regulatory and commercialization activities, and costs for ION357.

ION736 (FOXP3) (AZD8701) – ION736, is an investigational antisense medicine designed to reduce the production of Forkhead Box P3, or FOXP3, for the treatment of patients with cancer. FOXP3 is a protein involved in the function of immuno-suppressive T regulatory cells (Tregs). Tregs, which are found at high levels in various types of cancers, often predict poor survival and poor response to immune checkpoint therapeutics. Preclinical studies have demonstrated that FOXP3 downregulation resulted in an increased immune response and anti-tumor activity. Moreover, the combination of antisense inhibition of FOXP3 with other immuno-oncology drugs led to enhanced anti-tumor activity.

In August 2020, AstraZeneca initiated a first-in-human open label study of ION736 in patients with select advanced solid tumors. The study is a multi-center, open label multi-arm study in approximately 123 patients designed to evaluate the efficacy, safety and tolerability of ION736 administered intravenously as monotherapy and in combination with durvaluamb (MEDI4736) in patients with advanced solid tumors.

In the second quarter of 2020, we licensed ION736 to AstraZeneca. As a result, AstraZeneca is responsible for global development, regulatory and commercialization activities, and costs for ION736.

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

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. IONIS-AR-2.5$_{Rx}$ had a safety and tolerability profile supportive of continued development.

In March 2017, we licensed IONIS-AR-2.5$_{Rx}$ to Suzhou-Ribo to develop and commercialize the medicine in China. In the third quarter of 2021, we entered into a license agreement with Flamingo Therapeutics for the development and commercialization of certain programs from Ionis' oncology pipeline, including IONIS-AR-2.5$_{Rx}$ outside of China.

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

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

In the third quarter of 2021, we entered into a license agreement with Flamingo Therapeutics for the development and commercialization of certain programs from Ionis' oncology pipeline, including danvatirsen.

Phase 1 Medicines in Clinical Development

Our early-stage pipeline is comprised of medicines to treat a number of diseases, including from our cardiovascular franchise. It includes medicines based on our latest technology advancements. As we continue to add new investigational medicines to our pipeline, we believe these medicines have the potential to expand our mid and late-stage pipelines.

IONIS CLINICAL PIPELINE – PHASE 1

MEDICINES	INDICATION	PARTNER	PHASE 1
CARDIOVASCULAR			
ION904 (Angiotensinogen)	Uncontrolled hypertension	Ionis	
ION547 (FXII)	Thrombotic disorders	Ionis	
OTHER MEDICINES			
ION532 (APOL1)	Chronic kidney disease	AstraZeneca	
ION839 (PNPLA3)	NASH	AstraZeneca	
ION455	NASH	AstraZeneca	
Frenlosirsen (IRF4)	Cancer	Flamingo	
ION537 (YAP1)	Cancer	MD Anderson	

Antisense Technology

Our antisense technology is an innovative platform for discovering first-in-class and/or best-in-class medicines. 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 other drug discovery technologies.

These advantages include:

- Direct intervention in the disease process at the genetic level by targeting RNA: antisense technology represents a direct route from gene to drug. The explosion in genomic information and RNA biology has led to the discovery of many new disease-causing proteins and RNAs and has created new opportunities that are uniquely accessible by antisense technology.
- Precise specificity: we design antisense medicines to target a single RNA, minimizing the possibility of binding to unintended targets, which can cause unwanted side effects.
- Good drug properties: antisense medicines distribute well throughout the body. They also have a long half-life, in the range of weeks to months, which means patients and/or healthcare providers can dose our medicines weekly, monthly or even less frequently depending on the medicine and target tissue.
- Ability to combine with other medicines: because antisense medicines do not interact with the enzymes that metabolize or break down other medicines, physicians can use our medicines in combination with other medicines.
- Broad applications to multiple disease targets, multiple tissues and multiple mechanisms: there are virtually no “undruggable” targets with antisense technology.
- Efficient discovery and early development: because of the efficiency of our antisense technology, our drug discovery and early development costs and success rates compare favorably to small molecule or antibody drug discovery and development.

We develop antisense medicines we believe will pioneer new markets and change standards of care. Our areas of focus include cardiovascular and neurological diseases.

Technology Overview

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

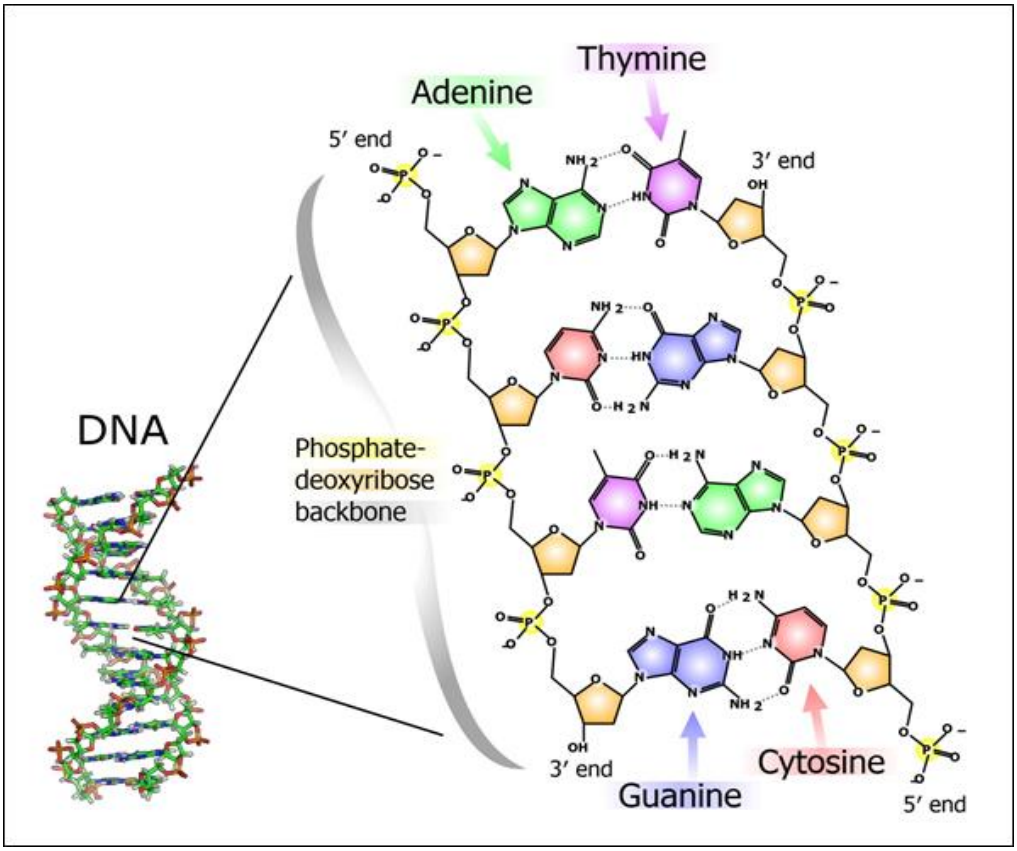


Figure 1: Illustration of DNA.

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

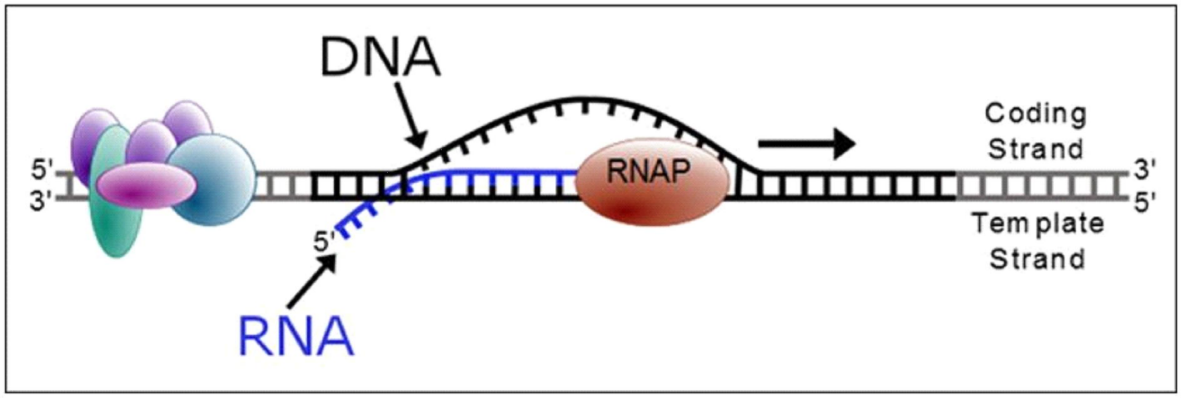


Figure 2: Transcription of information contained in a gene, or DNA, to RNA.

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

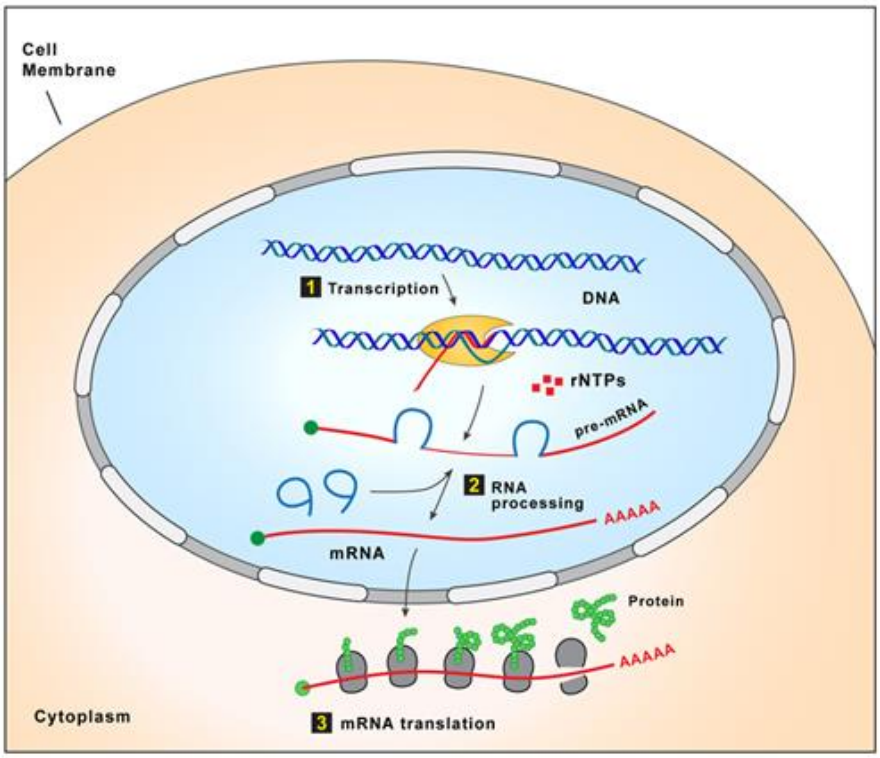


Figure 3: Translation of the protein-coding information contained in mRNA to protein.

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

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

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

LICA is a chemical technology we developed that involves attaching a molecule called a ligand that binds with receptors on the surfaces of cells in a highly specific manner. Because these receptors are often found only on certain cell types, LICA allows us to increase effective delivery of our antisense medicines with higher specificity to certain cell types that express these receptors relative to non-conjugated antisense medicines. As of December 2021, we have an integrated assessment of data from multiple LICA medicines and clinical programs which demonstrates that our LICA technology for liver targets can increase potency by 20-30-fold over our non-LICA antisense medicines.

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

We can also combine our LICA technology with our Generation 2.5 chemistry, further increasing potency. In addition to the LICA technology for liver targets, we are also developing LICA conjugation technology that we can use to target other tissues, such as pancreas and muscle, and initial results in animals are promising.

Antisense Targets and Mechanisms

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

When using antisense technology to inhibit the production of disease-causing proteins or reduce levels of harmful RNAs, our antisense medicines bind to the target RNA via highly specific nucleotide pairing, or hybridization, and recruit a cellular enzyme called ribonuclease H1, or RNase H1, to degrade the target RNA. The antisense medicine itself remains intact during this process, so it can remain active against additional target RNA molecules and repeatedly trigger their degradation (Figure 4). Examples of our antisense medicines that use the RNase H1 mechanism to reduce disease protein production include, TEGSEDI, WAYLIVRA, eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, tofersen and others.

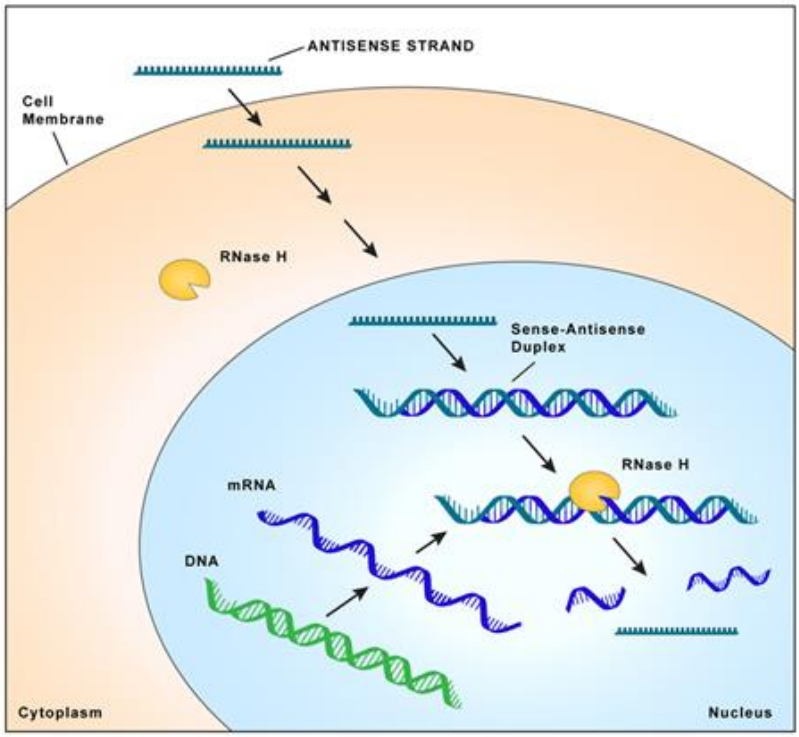


Figure 4: Antisense medicine using the RNase H mechanism of action.

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.

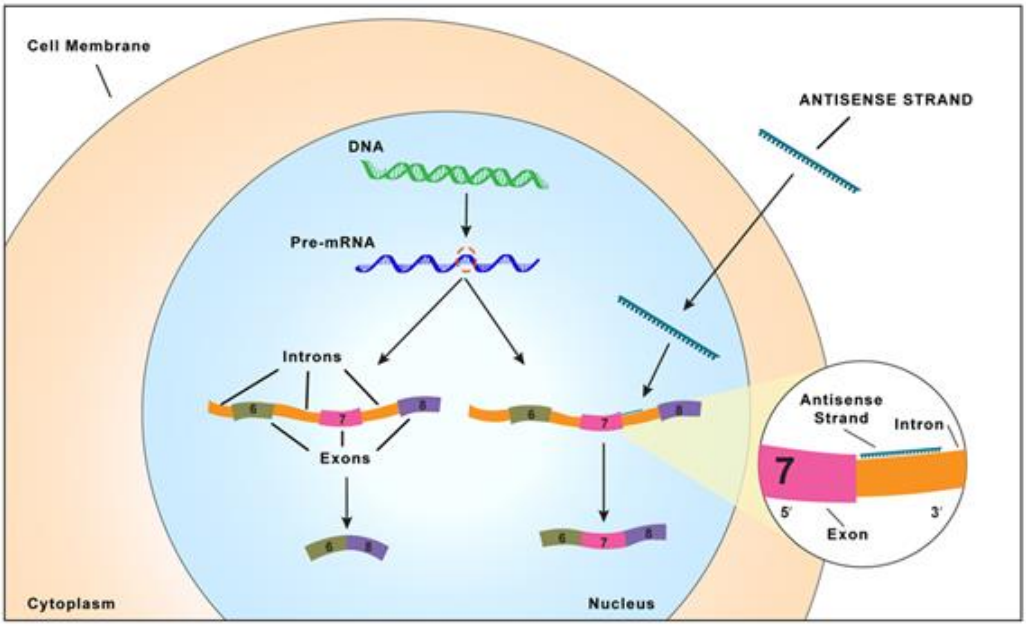


Figure 5: Antisense medicine altering splicing of the SMN2 mRNA.

We are also making progress in designing antisense medicines to target long, non-coding RNAs, or lncRNAs and RNAs that possess a toxic function in human diseases. Many of these RNAs, such as lncRNAs, do not make proteins but often cause disease by regulating the function of other genes or proteins. In 2014, we published a paper in *Nature* in which we were the first to show that targeted reduction of a lncRNA with an antisense compound can ameliorate certain cognitive deficits in a mouse model of Angelman syndrome, or AS. In 2021, we initiated the HALOS study, a Phase 1/2a study of ION582 in patients with AS.

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

Collaborative Arrangements

We have established alliances with a cadre of leading global pharmaceutical companies. Our partners include the following companies, among others: AstraZeneca, Bayer, Biogen, GSK, Novartis, and Roche. Through our partnerships, we have earned both commercial revenue and a broad and sustaining base of R&D revenue in the form of license fees, upfront payments and milestone payments. In 2021, we recognized $810 million in revenue, the majority of which was from our partnered medicines and programs. We have the potential to earn more than $24 billion in future milestone payments, licensing fees and other payments from our current partnerships. In addition, we are eligible to receive up to mid-20 percent royalties under certain partnerships. Below, we include the significant terms of our collaboration agreements. For additional details, including other financial information, see Note 6, *Collaborative Arrangements and Licensing Agreements*, in the Notes to the Consolidated Financial Statements.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with SMA. We and Biogen are currently developing nine investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development to treat people with ALS, SMA, AS, Alzheimer's disease and Parkinson's disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through December 2021, we have received $3.2 billion from our Biogen collaborations.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. From inception through December 2021, we generated more than $1.6 billion in total revenue under our SPINRAZA collaboration, including nearly $1.2 billion in revenue from SPINRAZA royalties and more than $435 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Biogen is responsible for global development, regulatory and commercialization activities and costs for SPINRAZA.

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a $25 million upfront payment in December 2017. In December 2021, we earned a $60 million license fee payment when Biogen exercised its option to license ION306. Biogen is solely responsible for the costs and expenses related to the development, manufacturing and potential future commercialization of ION306 following the option exercise.

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 $555 million if Biogen advances ION306. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration.

Neurology Collaborations

2018 Strategic Neurology

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

In June 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at an approximately 25 percent cash premium and $375 million in an upfront payment. We are eligible to receive up to $270 million in milestone payments for each medicine that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration. We are currently advancing nine programs under this collaboration and through December 2021, we have generated nearly $1.1 billion in payments, including $23 million in milestone payments generated in 2021 when Biogen advanced three programs under this collaboration.

2013 Strategic Neurology

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

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed under this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and milestone payments. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that Biogen successfully commercializes under this collaboration. Through December 2021, we have generated over $280 million under this collaboration, including $10 million we received from Biogen in 2021 when Biogen advanced ION541, an investigational medicine targeting ATXN2 to treat patients with ALS.

2012 Neurology

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

Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that Biogen successfully commercializes under this collaboration. Through December 2021, we have generated over $165 million under our collaboration, including $10 million we received from Biogen for advancing ION582 during 2021.

Joint Development and Commercialization Arrangement

AstraZeneca

Eplontersen Collaboration

In December 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. We are jointly developing and preparing to commercialize eplontersen with AstraZeneca in the U.S. AstraZeneca obtained exclusive rights to commercialize eplontersen outside the U.S., except certain countries in Latin America. Under the terms of the agreement, we received a $200 million upfront payment. We are eligible to receive up to $485 million in development and approval milestones, and up to $2.9 billion in sales-related milestone payments. In addition, we are eligible to receive up to mid-20 percent royalties for sales in the U.S. and tiered royalties up to the high teens for sales outside the U.S.

The collaboration also includes territory-specific development, commercial and medical affairs cost-sharing provisions. AstraZeneca will pay 55 percent of the costs associated with the ongoing global Phase 3 development program. As we will continue to lead the Phase 3 development program, we will recognize as revenue the 55 percent of cost-share funding AstraZeneca is responsible for in the same period we incur the related development expenses. As AstraZeneca is responsible for the majority of the commercial and medical affairs costs in the U.S. and all costs associated with bringing eplontersen to market outside the U.S., we will recognize cost-share funding we receive from AstraZeneca related to these activities as a reduction of our commercial and medical affairs expenses. Through December 2021, we have generated $200 million in payments under this collaboration.

Research and Development Partners

AstraZeneca

In addition to our collaboration for eplontersen, we have two other collaborations with AstraZeneca. One is focused on the treatment of cardiovascular, renal and metabolic diseases and the other is focused on the treatment of oncology diseases. We and AstraZeneca are currently developing six medicines under these collaborations. From inception through December 2021, we have generated nearly $425 million from our AstraZeneca research and development collaborations.

Cardiovascular, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiovascular, renal and metabolic diseases. Under our collaboration, AstraZeneca has licensed five medicines from us. AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for each of the medicines it has licensed.

Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than $5.5 billion as medicines under this collaboration advance. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. Through December 2021, we have generated over $280 million in payments, including $40 million we earned in 2021 for two targets that AstraZeneca is advancing for a metabolic disease.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense medicines to treat cancer. We and AstraZeneca also established an oncology research program. In 2020, AstraZeneca licensed ION736, an investigational medicine in development targeting FOXP3 for the treatment of cancer. AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for ION736.

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive license fees and milestone payments of up to more than $265 million as this collaboration advances. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. Through December 2021, we have generated over $140 million in payments under this collaboration, including $13 million we earned in 2020 when AstraZeneca licensed ION736.

Bayer

In May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis and we received a $100 million upfront payment. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of fesomersen (formerly IONIS-FXI-L$_{Rx}$), which Bayer licensed. In conjunction with the amendment, we received a $75 million payment. In October 2019, Bayer decided to advance fesomersen following positive clinical results. Bayer is now responsible for all global development, regulatory and commercialization activities and costs for the FXI program. We are eligible to receive additional milestone payments as the FXI program advances toward the market. Over the term of the collaboration, we are eligible to receive up to $385 million in license fees, milestone payments and other payments. In addition, we are eligible to receive tiered royalties in the low to high 20 percent range on gross margins of both medicines combined. Through December 2021, we have generated over $190 million under this collaboration.

GSK

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

Under our agreement, if GSK successfully develops bepirovirsen and achieves pre-agreed sales targets, we could receive license fees and milestone payments of more than $260 million. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that GSK successfully commercializes under this alliance. Through December 2021, we have generated over $185 million in payments under our collaboration.

Novartis

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

Under the collaboration, we are eligible to receive up to $675 million in milestone payments related to pelacarsen. We are also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of pelacarsen. Through December 2021, we have generated nearly $425 million under our collaboration including an upfront payment, license fee, milestone payments and other payments from this collaboration, including a $25 million milestone payment we earned in 2021 when Novartis achieved 50 percent enrollment in the Lp(a) HORIZON Phase 3 cardiovascular outcome study of pelacarsen.

In conjunction with this collaboration, we entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for $100 million in the first quarter of 2017.

Roche

Huntington's Disease

In April 2013, we formed an alliance with Hoffman-La Roche Inc. and F. Hoffmann-La Roche Ltd., collectively Roche, to develop treatments for HD based on our antisense technology. Under the agreement, we discovered and developed tominersen, an investigational medicine targeting HTT protein. We developed tominersen through completion of our Phase 1/2 clinical study in people with early stage HD. In December 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen and is now responsible for the global development, regulatory and commercialization activities and costs for tominersen. In March 2021, Roche discontinued dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest Huntington's disease based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded Independent Data Monitoring Committee. In January 2022, Roche announced it is actively preparing to initiate a new Phase 2 study of tominersen in patients with HD. Post-hoc analyses from the GENERATION HD1 study suggested tominersen may benefit younger adult patients with lower disease burden.

Under the terms of the agreement, we received an upfront payment of $30 million in April 2013. We are eligible to receive up to $365 million in a license fee and milestone payments as tominersen advances. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional medicine successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on net sales from any product resulting from this alliance. Through December 2021, we have generated $150 million under our collaboration.

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

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

Under the terms of this agreement, we received a $75 million upfront payment in October 2018. We are eligible to receive more than $680 million including a license fee and milestone payments. In addition, we are also eligible to receive tiered royalties from the high teens to twenty percent on net sales. Through December 2021, we have generated over $75 million under our collaboration.

Commercialization Partnerships

Swedish Orphan Biovitrum AB (Sobi)

We began commercializing TEGSEDI and WAYLIVRA in Europe in January 2021 and TEGSEDI in North America in April 2021 through distribution agreements with Sobi. Under our agreements, we are responsible for supplying finished goods inventory to Sobi and Sobi is responsible for selling each medicine to the end customer. In exchange, we earn a distribution fee on net sales from Sobi for each medicine.

PTC Therapeutics

In August 2018, we entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. Under the license agreement, we are eligible to receive royalties from PTC in the mid-20 percent range on net sales for each medicine. In December 2021, we started receiving royalties from PTC for TEGSEDI sales.

Technology Enhancement Collaboration

Bicycle License Agreement

In December 2020, we entered into a collaboration agreement with Bicycle and obtained an option to license its peptide technology to potentially increase the delivery capabilities of our LICA medicines. In July 2021, we paid $42 million when we exercised our option to license Bicycle's technology, which included an equity investment in Bicycle. As part of our stock purchase, we entered into a lockup agreement with Bicycle that restricts our ability to trade our Bicycle shares for one year. In 2021, we recorded a $7 million equity investment for the shares we received in Bicycle. We recognized the remaining $35 million as R&D expense in 2021. From inception through December 2021, we have paid Bicycle $47 million under this collaboration agreement.

Other Agreements

Alnylam Pharmaceuticals, Inc.

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

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

The Ludwig Institute; Center for Neurological Studies

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

Manufacturing

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

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

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

We believe we have sufficient manufacturing capacity at our own facility or at contract manufacturing organizations, or CMOs, to meet our current internal research, development and potential commercial needs, as well as our obligations under existing agreements with our partners for research, development and commercial material. As we continue to advance our wholly owned medicines through Phase 3 development, we will begin to manufacture process performance qualification batches and pre-approval inspection batches of our Phase 3 medicines that may be used for regulatory submissions and, pending regulatory approval, commercial sale. We believe our current network of CMO partners are capable of providing sufficient quantities to meet anticipated commercial demands. Additionally, we continue to evaluate relationships with additional suppliers to increase overall capacity and diversify our supply chain. While we believe that there are alternate sources of supply that can satisfy our commercial requirements, it is possible that identifying and establishing relationships with such sources, if necessary, could result in significant delay or material additional costs. We also could experience a disruption in supply from our current CMO partners.

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

Specifically, we have the following in place for our approved medicines, SPINRAZA, TEGSEDI and WAYLIVRA and our medicines in Phase 3 development: eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen.

SPINRAZA

Biogen is responsible for SPINRAZA drug supply.

TEGSEDI and WAYLIVRA

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

Eplontersen

Our CMO partner supplied the API and the finished drug product for eplontersen's Phase 3 program. Pursuant to our collaboration with AstraZeneca, we will manufacture and supply eplontersen through a CMO for the ongoing clinical trials and process qualifications. AstraZeneca is responsible for commercial supply.

Olezarsen, Donidalorsen, ION363

We have supplied the API and the finished drug product for olezarsen, donidalorsen and ION363 that we believe will be sufficient through the completion of the Phase 3 programs for each medicine. We plan to leverage our relationships with CMOs to procure long-term raw material and drug supplies at competitive prices in the future.

Pelacarsen

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

Tofersen

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

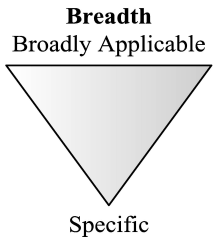
Patents and Proprietary Rights

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

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

Type of Patent Claim
(Broadly Applicable to Specific)

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



Chemically Modified Nucleosides and Oligonucleotides

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

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

Antisense Drug Design Motifs

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

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

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

LIgand-Conjugated Antisense (LICA) Technology

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

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

Therapeutic Methods of Treatment and Antisense Drug Sequences

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

SPINRAZA and Survival Motor Neuron

We believe SPINRAZA is protected from generic competition in the U.S. until at least 2035 and in Europe until at least 2030 by a suite of patents. These issued patents include: (i) patents licensed from the University of Massachusetts drawn to antisense compounds having the sequence of SPINRAZA, independent of chemical modification and uses of such compounds for treating SMA, and (ii) joint patents with Cold Spring Harbor Laboratory claiming fully modified 2'MOE compositions targeting SMN2, including the precise composition of matter of SPINRAZA and methods of using such compositions. We have filed for patent term extension, to potentially extend the term beyond 2030. With Biogen's license of SPINRAZA, we assigned our interest in these patents to Biogen. The table below lists some key issued patents protecting SPINRAZA in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	10,266,822	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2025	Methods of increasing exon-7 containing SMN2 mRNA in a cell using an oligonucleotide having the sequence of SPINRAZA
United States	8,110,560	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2025	Methods of using antisense oligonucleotides having sequence of SPINRAZA to alter splicing of SMN2 and/or to treat SMA
Europe	1910395	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Sequence and chemistry (full 2'-MOE) of SPINRAZA
Europe	3308788	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2026	Pharmaceutical compositions that include SPINRAZA
United States	7,838,657	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	2027	Oligonucleotides having sequence of SPINRAZA
United States	8,361,977	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	2030	Sequence and chemistry (full 2'-MOE) of SPINRAZA
United States	8,980,853	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Methods of administering SPINRAZA
United States	9,717,750	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Methods of administering SPINRAZA to a patient
Europe	3449926	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Pharmaceutical compositions that include SPINRAZA for treating SMA
Europe	3305302	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2030	Antisense compounds including SPINRAZA for treating SMA
United States	9,926,559	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	2034	SPINRAZA doses for treating SMA
United States	10,436,802	METHODS FOR TREATING SPINAL MUSCULAR ATROPHY	2035	SPINRAZA dosing regimen for treating SMA

TEGSEDI and Transthyretin

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

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

WAYLIVRA and Apolipoprotein C-III

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

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

Eplontersen and Transthyretin

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

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	10,683,499	COMPOSITIONS AND METHODS FOR MODULATING TTR EXPRESSION	2034	Composition of eplontersen
Europe	3524680	COMPOSITIONS AND METHODS FOR MODULATING TTR EXPRESSION	2034	Composition of eplontersen

Olezarsen and ApoC-III

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

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

Donidalorsen and PKK

We believe donidalorsen is protected from generic competition in the U.S. and Europe until at least 2035. Additional patent applications to protect donidalorsen in other foreign jurisdictions are being pursued. The table below lists some key issued patents protecting donidalorsen in the U.S. and Europe.

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	9,315,811	METHODS FOR MODULATING KALLIKREIN (KLKB1) EXPRESSION	2032	Methods of treating HAE
Europe	2717923	METHODS FOR MODULATING KALLIKREIN (KLKB1) EXPRESSION	2032	Compounds for use in treating an inflammatory condition, including HAE
United States	10,294,477	COMPOSITIONS AND METHODS FOR MODULATING PKK EXPRESSION	2035	Composition of donidalorsen
Europe	3137091	COMPOSITIONS AND METHODS FOR MODULATING PKK EXPRESSION	2035	Composition of donidalorsen

ION363 and FUS

Patent applications designed to protect ION363 from generic competition are being pursued in the U.S. and Europe; patents issuing from these applications would have term until at least 2040. The table below lists some key pending patent applications designed to protect ION363 in the U.S. and Europe:

Jurisdiction	Application No.	Title	Expiration	Description of Claims
United States	17/613,183	COMPOUNDS AND METHODS FOR REDUCING FUS EXPRESSION	2040	Composition of ION363
Europe	20815459.1	COMPOUNDS AND METHODS FOR REDUCING FUS EXPRESSION	2040	Composition of ION363

Pelacarsen and Apo(a)

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

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

Tofersen and SOD-1

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

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	10,385,341	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Composition of tofersen
United States	10,669,546	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Methods of treating a SOD-1 associated neurodegenerative disorder by administering tofersen
United States	10,968,453	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Methods of treating a SOD-1 associated neurodegenerative disorder by administering a pharmaceutical composition of tofersen
Europe	3126499	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Composition of tofersen

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

Manufacturing Patents

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

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

Government Regulation

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

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

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

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

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

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

In addition, the distribution of prescription pharmaceutical products is subject to the Drug Supply Chain Security Act, or DSCA, which regulates the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

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

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

Sales and Marketing

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

In the U.S. sales, marketing and scientific/educational programs must also comply with various federal and state laws pertaining to healthcare "fraud and abuse," including anti-kickback laws and false claims laws. Anti-kickback laws make it illegal for a prescription drug manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug. Due to the breadth of the statutory provisions, limited statutory exceptions and regulatory safe harbors, and the absence of guidance in the form of regulations and very few court decisions addressing industry practices, it is possible that our practices might be challenged under anti-kickback or similar laws. Moreover, recent healthcare reform legislation has strengthened these laws. For example, the Patient Protection and Affordable Act, as amended by the Health Care and Education Reconciliation Act of 2010, or Affordable Care Act, among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes to clarify that a person or entity does not need to have actual knowledge of this statute or specific intent to violate it. In addition, the Affordable Care Act clarifies that the government may assert that a claim that includes items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the false claims statutes. False claims laws prohibit anyone from knowingly and willingly presenting, or causing to be presented for payment, to third-party payers (including Medicare and Medicaid) claims for reimbursed drugs or services that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. Our activities relating to the sale and marketing of our drugs may be subject to scrutiny under these laws. Violations of fraud and abuse laws may be punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid) and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties also can be imposed upon executive officers and employees, including criminal sanctions against executive officers under the so-called "responsible corporate officer" doctrine, even in situations where the executive officer did not intend to violate the law and was unaware of any wrongdoing.

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

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

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

Both the federal and state governments in the U.S. and foreign governments continue to propose and pass new legislation and regulations designed to contain or reduce the cost of healthcare. For example, in July 2021, the Biden administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In response to Biden’s executive order, on September 9, 2021, the U.S. Department of Health and Human Services, or HHS, released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. Congress is also considering additional health reform measures. Such legislation and regulations may result in decreased reimbursement, which may further exacerbate industry-wide pressure to reduce the prices charged for medical products.

Competition

Our Business in General

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

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

Below we have included what we believe to be the competitive landscape for our marketed medicines and for the medicines we currently have in Phase 3 trials. We have included medicines that we believe compete or may compete directly with our medicines. We included competitors, potential competitors that are past Phase 1 development or potential competitors that plan to start a pivotal study this year. We do not believe that any medicines meet these criteria to compete with ION363.

SPINRAZA

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

Medicine	**Company**	**Medicine Description** (1)	**Phase** (1)	**Route of Administration** (1)
Zolgensma (Onasemnogene abeparvovec)	Novartis	Gene therapy targeting the genetic root cause of SMA by replacing the missing or nonworking SMN1 gene	Approved for pediatric SMA patients less than 2 years of age	Intravenous infusion
Evrysdi (Risdiplam)	Roche	A small molecule medicine that modulates splicing of the SMN2 gene	Approved for SMA patients of 2 months or older	Oral

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

TEGSEDI and Eplontersen

We consider the following medicines as competitors and potential future competitors to TEGSEDI and eplontersen for the indication of hATTR amyloidosis and/or ATTR cardiomyopathy:

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

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

WAYLIVRA and Olezarsen

We believe that the following medicines could compete with WAYLIVRA and olezarsen in FCS and SHTG:

Medicine	Company	Medicine Description (1)	Phase (1)	Route of Administration (1)
ARO-APOC3	Arrowhead Pharmaceuticals	Targets APOCIII by utilizing Targeted RNAi Molecule Platform	3 (FCS), 2 (SHTG)	Subcutaneous Injection
Lomitapide	Amryt Pharma	Microsomal triglyceride transfer protein (MTP) inhibitor	2 (FCS) (investigator led)	Oral
Evinacumab	Regenerion	ANGPTL3 mAb	2 (SHTG)	Intravenous Infusion
BIO89-100	Bio 89	FGF21 analog	2 (SHTG)	Subcutaneous Injection

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

Donidalorsen

We believe that the following medicines could compete with donidalorsen as a prophylactic treatment for patients with HAE:

Medicine	Company	Medicine Description (1)	Phase (1)	Route of Administration (1)
Takhzyro (lanadelumab-flyo)	Takeda	A monoclonal antibody that inhibits plasma kallikrein activity	Approved for HAE patients 12 years and older	Subcutaneous Infusion
Cinryze (C1-esterase inhibitor)	Takeda	A human plasma protein that mediates inflammation and coagulation	Approved for HAE patients 6 years and older	Intravenous Infusion
Orladeyo (berotralstat)	BioCryst	Oral plasma kallikrein inhibitor	Approved for HAE patients 12 years and older	Oral
Haegarda (C1 esterase inhibitor)	CSL Behring	C1 esterase inhibitor	Approved for HAE patients 6 years and older	Subcutaneous Infusion
garadacimab	CSL Behring	An anti-factor XIIa monoclonal antibody	3	Subcutaneous Infusion
KVD824	KalVista	Oral plasma kallikrein inhibitor	2	Oral
NTLA-2002	Intellia	CRISPR therapeutic candidate designed to inactivate the kallikrein B1 gene	1/2	Intravenous Infusion

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

Pelacarsen

We believe that the following medicine could compete with pelacarsen in CVD in patients with elevated LP(a):

Medicine	Company	Medicine Description (1)	Phase (1)	Route of Administration (1)
AMG 890	Amgen/ Arrowhead Pharmaceuticals	RNAi therapeutic designed to lower Lp(a)	2	Subcutaneous Injection

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

Tofersen

We believe that the following medicines could compete with tofersen in SOD1-ALS:

Medicine	Company	Medicine Description (1)	Phase (1)	Route of Administration (1)
Arimoclomol	Orphazyme	Provides cellular protection from abnormal proteins by activating molecular “chaperone” proteins that can repair or degrade the damaged proteins	3	Oral
NI-204	Neurimmune	A human derived antibody targeting misfolded SOD1	2	Intravenous Infusion

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

Environmental, Social and Governance Initiatives

We recognize the importance of Environmental, Social and Governance, or ESG, initiatives as it relates to our business strategy and risk assessment. During 2020 and 2021, we took steps to formalize our corporate responsibility program. In December 2021, we issued our inaugural corporate responsibility report. As part of our ongoing work, we identified the following corporate responsibility initiatives that we believe are most important to our business:

- Safety of patients in clinical trials;
- Drug safety and supply chain management;
- Access to medicines and tackling devastating diseases;
- Human resources management;
- Diversity, equity and inclusion;
- Employee health and safety; and
- Governance and business ethics

We have a relatively small environmental footprint, so our stewardship programs focus on improving eco-awareness, identifying efficiencies and integrating more sustainable practices into our daily operations. Our priority assessment considered investor and other stakeholder interests and is aligned with the requirements of ESG ratings agencies and with leading ESG frameworks, including the Sustainability Accounting Standards Board, or SASB.

We encourage you to view our *2021 Corporate Responsibility Report* published on our website for more detailed information regarding our ESG initiatives. Nothing in the report or on our website shall be deemed incorporated by reference into this Annual Report on Form 10-K.

Employees & Human Capital

As of February 16, 2022, we employed 660 people, the vast majority of whom reside in the U.S. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Our average employee turnover rate in 2021 was 16 percent, while the turnover for life sciences/ medical device companies over this period was 19 percent according to a survey published by Radford – an Aon Hewitt Company. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is as critical to our future success as it has been to the success we have enjoyed to date.

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

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

Benefits

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

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

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

Pay Equity

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

In 2021, we engaged an independent third-party expert to perform a pay equity analysis that reviewed pay equity by gender, race and age. We plan to continue to engage a third-party expert to review pay equity every two to three years, as we determine necessary.

Diversity, Equity and Inclusion

At Ionis, we encourage diversity in our workforce. Prejudicial barriers to human potential and productivity are foreign to our values. We recognize that for the full potential of our workforce to be realized, we must cultivate an inclusive culture where all employees feel empowered to contribute fully in an environment that values different perspectives, leading to better ideas and increased innovation. We have several employee-led resource groups dedicated to different aspects of diversity and a diverse management team and board of directors.

Training and Development

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

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

Information about our Executive Officers

The following sets forth certain information regarding our executive officers as of February 16, 2022:

Name	Age	Position
Brett P. Monia, Ph.D.	60	Chief Executive Officer
Joseph T. Baroldi	44	Executive Vice President, Chief Business Officer
C. Frank Bennett, Ph.D.	65	Executive Vice President, Chief Scientific Officer
Onaiza Cadoret-Manier	57	Executive Vice President, Chief Product Strategy and Operations Officer
Richard S. Geary, Ph.D.	64	Executive Vice President, Chief Development Officer
Elizabeth L. Hougen	60	Executive Vice President, Finance and Chief Financial Officer
Patrick R. O'Neil, Esq.	48	Chief Legal Officer, General Counsel and Corporate Secretary
Eugene Schneider, M.D.	49	Executive Vice President, Chief Clinical Development Officer
Eric E. Swayze, Ph.D.	56	Executive Vice President, Research

BRETT P. MONIA, Ph.D.

Chief Executive Officer

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

JOSEPH T. BAROLDI

Executive Vice President, Chief Business Officer

Mr. Baroldi has served as Ionis' Executive Vice President, Chief Business Officer since January 2022. Prior to Ionis, Mr. Baroldi was the chief operating officer at Avidity Biosciences, a biotechnology company focused on oligonucleotide-based therapies. Prior to Avidity, Mr. Baroldi was vice president of Business Development and Alliance Management at Ionis from 2009 to 2020. Mr. Baroldi has also held positions in strategic planning and scientific research for Gen-Probe Inc. and Ionis.

C. FRANK BENNETT, Ph.D.

Executive Vice President, Chief Scientific Officer

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

ONAIZA CADORET-MANIER

Executive Vice President, Chief Product Strategy and Operations Officer

Ms. Cadoret-Manier has served as Ionis' Executive Vice President, Chief Product Strategy and Operations Officer since February 2022. From April 2020 to February 2022, Ms. Cadoret-Manier served as our Executive Vice President, Chief Corporate Development and Commercial Officer. Ms. Cadoret-Manier joined Ionis as Chief Corporate Development and Commercial Officer in January 2020. Prior to joining Ionis, from 2018 to 2019 Ms. Cadoret-Manier was the chief commercial officer for Grail Biosciences, an early detection genomics company. Prior to Grail, Ms. Cadoret-Manier was vice president of the Respiratory Franchise at Genentech where she worked from 2011 to 2018. Ms. Cadoret-Manier also has held multiple senior management positions overseeing corporate strategy, alliances, and marketing and sales for numerous disease areas for Genentech, Pfizer and Amylin Pharmaceuticals.

RICHARD S. GEARY, Ph.D.

Executive Vice President, Chief Development Officer

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

ELIZABETH L. HOUGEN

Executive Vice President, Finance and Chief Financial Officer

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

PATRICK R. O'NEIL, Esq.

Chief Legal Officer, General Counsel and Corporate Secretary

Mr. O'Neil has served as Ionis' Chief Legal Officer and General Counsel since September 2021. Mr. O'Neil also serves as our Corporate Secretary. From March 2020 to September 2021, Mr. O'Neil served as our Executive Vice President, Legal & General Counsel and Chief Compliance Officer. From January 2013 to March 2020, Mr. O'Neil served as our Senior Vice President, Legal and General Counsel. From September 2010 to January 2013, Mr. O'Neil served as our Vice President, Legal and General Counsel and from January 2009 to September 2010, he served as our Vice President, Legal and Senior Transactions Counsel. From October 2001 to January 2009 he held various positions within our Legal department. Prior to joining Ionis, Mr. O'Neil was an associate at Cooley LLP.

EUGENE SCHNEIDER, M.D.

Executive Vice President, Chief Clinical Development Officer

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

ERIC E. SWAYZE, Ph.D.

Executive Vice President, Research

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

Item 1A. RISK FACTORS

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

Risks Related to the COVID-19 Pandemic

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

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

In response to these public health directives and orders, in March 2020, we implemented work-from-home policies for most of our employees globally and generally suspended business-related travel. In the U.S., as vaccinations have become more widely available, states have lifted restrictions implemented as part of the pandemic response and reopened their economies. In June 2021, the Governor of California terminated the vast majority of executive actions that were put in place beginning in March 2020, leaving only a subset of provisions that facilitate the ongoing recovery. In May 2021, the Commonwealth of Massachusetts also lifted most of its pandemic restrictions. We continue to modify our policies for our employees in California, Massachusetts, and internationally to align with current local guidance. We believe the effects of these work-from-home and travel policies have had a limited impact on our business.

These public health directives and orders have impacted our and our partners' sales efforts. For example, some physician and hospital policies that have been put in place as a result of the COVID-19 Pandemic restrict in-person access by third parties, which has in some cases impacted our commercialization efforts for TEGSEDI and WAYLIVRA. Additionally, Biogen has reported that it is monitoring the demand for SPINRAZA, including the duration and degree to which it might see delays in starting new patients on SPINRAZA due to hospitals diverting resources necessary to administer SPINRAZA to care for COVID-19 patients. These and similar, and perhaps more severe, disruptions in our or our partner's commercial operations could materially impact our business, operating results and financial condition in the future.

Quarantines, shelter-in-place, executive and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations could occur, could impact personnel at third-party manufacturing facilities in the U.S. and other countries, or the availability or cost of materials, which would disrupt our supply chain. Recently there have been major disruptions to the global supply chain due to the COVID-19 Pandemic. To date, we have not experienced any significant consequences to our business as a result of the current supply chain disruptions, but could in the future if such disruptions persist or worsen.

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

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

In addition, some of our partners have experienced impacts to their clinical trial operations as a result of the COVID-19 Pandemic. For example, in December 2021, Novartis announced that enrollment for the Phase 3 HORIZON study had been delayed due to the COVID-19 Pandemic.

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

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

Risks Related to the Commercialization of our Medicines

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

We have limited experience as a company in commercializing medicines and we will have to invest significant financial and management resources to develop the infrastructure required to successfully commercialize our medicines. There are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. We will also need to scale-up existing internal support functions to aid our commercialization efforts, in particular, regulatory affairs and medical affairs. Any failure to effectively build or maintain the infrastructure required to successfully commercialize our medicines, including our sales, marketing, market access, distribution, and related capabilities, or scale-up our existing support functions, could adversely impact the revenue we generate from our medicines. In addition, if we choose to rely on third parties to assist us in commercializing our medicines, we may not be able to enter into collaborations or hire consultants or external service providers on acceptable financial terms, or at all. If we do engage third parties to assist us in the commercialization of our medicines, our product revenues and profitability may be lower than if we commercialized such medicines ourselves.

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

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

Additionally, in many of the markets where we or our partners may sell our medicines in the future, if we or our partners cannot agree with the government or other third-party payers regarding the price we can charge for our medicines, then we may not be able to sell our medicines in that market. Similarly, cost control initiatives by governments or third-party payers could decrease the price received for our medicines or increase patient coinsurance to a level that makes our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development, economically unviable. If the pricing of any of our medicines decreases for any reason, it will reduce our revenue for such medicine. For example, Biogen has disclosed that SPINRAZA revenue has decreased in part due to lower pricing in the U.S. and certain rest of world markets.

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

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

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

For example, TEGSEDI requires periodic blood and urine monitoring, is available in the U.S. only through a REMS program, and the product label in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis. Our main competition in the U.S. market for TEGSEDI is patisiran, marketed by Alnylam Pharmaceuticals, Inc. Although patisiran requires intravenous administration and pre-treatment with steroids, it does not have a boxed warning nor is it available only through a REMS program. Additionally, the product label for WAYLIVRA in the EU requires regular blood monitoring. In each case, these label requirements have negatively affected our ability to attract and retain patients for these medicines. If we or our partner cannot effectively maintain patients on TEGSEDI or WAYLIVRA, including due to limitations or restrictions on the ability to conduct periodic blood and urine monitoring of our patients as a result of the current COVID-19 Pandemic, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

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

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

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

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

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

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

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

- Onasemnogene abeparvovec and risdiplam compete with SPINRAZA;
- Patisiran, tafamidis, and tafamidis meglumine compete with TEGSEDI and could compete with eplontersen;
- Vutrisiran and acoramidis could compete with TEGSEDI and eplontersen;
- ARO-APOC3, lomitapide, evinacumab, BIO89-100, and gemcabene could compete with WAYLIVRA and olezarsen;
- AMG890 could compete with pelacarsen;
- Arimoclomol, ultomiris, mastinib and trehalose could compete with tofersen; and
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, KVD824, and NTLA-2002 could compete with donidalorsen.

SPINRAZA injection for intrathecal use is an antisense medicine indicated for the treatment of SMA patients of all ages approved in over 50 countries. Specifically, SPINRAZA faces competition from onasemnogene abeparvovec, a gene therapy product that was approved in the U.S. in May 2019 and in the EU in May 2020 for the treatment of SMA, as well as risdiplam, an oral product for the treatment of SMA that was approved in the U.S. in August 2020 and in the EU in March 2021. Biogen has disclosed that SPINRAZA revenue has decreased primarily due to a reduction in demand as a result of increased competition and that future sales of SPINRAZA may be adversely affected by competing products.

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

Our medicines could be subject to regulatory limitations following approval.

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

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

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

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

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

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

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

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

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

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

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

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

We depend on our collaboration with AstraZeneca for the joint development and commercialization of eplontersen.

We have entered into a collaborative arrangement with AstraZeneca to develop and commercialize eplontersen. Under the terms of the collaboration agreement, Ionis and AstraZeneca will co-develop and co-commercialize eplontersen in the U.S. and AstraZeneca will have the sole right to commercialize eplontersen in all other countries. Prior to co-commercializing eplontersen in the U.S., we will need to negotiate a co-commercialization agreement with AstraZeneca to govern the parties' performance of co-commercialization, which agreement will include a commercial plan and budget. As a company we do not have experience with co-commercialization arrangements. We also do not have control over the amount and timing of resources that AstraZeneca devotes to our collaboration, particularly outside of the U.S. If the co-commercialization arrangement for eplontersen is not successful for any reason, eplontersen may not meet our commercial objectives and our revenues for eplontersen may be limited.

In addition, a Joint Steering Committee, or JSC, having equal membership from us and AstraZeneca, and various subcommittees oversee and coordinate the development, manufacturing, commercialization and other exploitation activities for eplontersen in the U.S. by mutual agreement. If any subcommittee cannot reach unanimous agreement on any matter within its respective scope of authority, such matter may be referred to the JSC for resolution. If the JSC cannot come to a mutual agreement on any particular matter, this could delay our ability to develop or commercialize eplontersen.

We are relying on third parties to market, sell and distribute TEGSEDI and WAYLIVRA.

We have entered into agreements with third parties to commercialize TEGSEDI and WAYLIVRA as follows:

- In April 2021, we entered into a distribution agreement with Sobi to commercialize TEGSEDI in the U.S. and Canada;
- In December 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe; and
- In August 2018, we granted PTC the exclusive right to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries.

We are relying on Sobi and PTC to effectively market, sell and distribute TEGSEDI and WAYLIVRA and have less control over sales efforts and may receive less revenue than if we commercialized TEGSEDI or WAYLIVRA by ourselves. If Sobi or PTC does not successfully commercialize TEGSEDI or WAYLIVRA, including as a result of delays or disruption caused by the current COVID-19 Pandemic, we may receive limited revenue for TEGSEDI or WAYLIVRA in the U.S., Canada, Europe, Latin America or certain Caribbean countries, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

Our operations are subject to additional healthcare laws.

Our operations are subject to additional healthcare laws, including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws, which are subject to change at any time. For example, in November 2020, the U.S. Department of Health and Human Services issued a final rule modifying the anti-kickback law safe harbors for Medicare Part D plans, pharmacies, and pharmaceutical benefit managers. Efforts to ensure that our operations comply with current applicable healthcare laws and regulations involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. Penalties for violations of applicable healthcare laws and regulations may include significant civil, criminal and administrative penalties, damages, disgorgement, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and additional reporting requirements and oversight if we enter into a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws. In addition, violations may also result in reputational harm, diminished profits and future earnings.

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

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

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the U.S., no uniform policy of coverage and reimbursement for medicines exists among third-party payers. Therefore, coverage and reimbursement for medicines can differ significantly from payer to payer. For example, the Affordable Care Act was passed in March 2010, and substantially changed the way healthcare is financed by both governmental and private insurers, and continues to significantly impact the U.S. pharmaceutical industry. There have been judicial and Congressional challenges to certain aspects of the Affordable Care Act, as well as efforts to repeal or replace certain aspects of the Affordable Care Act. It is unclear how future litigation and healthcare reform measures will impact the Affordable Care Act and our business.

Further, we believe that future coverage, reimbursement and pricing will likely be subject to increased restrictions both in the U.S. and in international markets. In the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries, legislation and executive orders designed to, among other things, reduce drug prices (e.g., by supporting drug price negotiation in Medicare Parts B and D, with those negotiated prices also available to commercial plans, and progressing legislation to slow price increases over time on existing drugs), increase competition (e.g., by supporting legislation to speed the entry of biosimilar and generic drugs, including shortening the period of exclusivity, policies in Medicare Part B to increase the prescribing of biosimilars by physicians, and a prohibition on “pay-for-delay” agreements and anti-competitive practices by drug manufacturers), lower out-of-pocket drug costs for patients (e.g., by capping Medicare Part D beneficiary out-of-pocket pharmacy expenses), and foster scientific innovation to promote better health care and improved health (e.g., by investing in public and private research and incentivizing the market to promote discovery of valuable and accessible new treatments). At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Third-party coverage and reimbursement for medicines may not be available or adequate in either the U.S. or international markets, and third-party payers, whether foreign or domestic, or governmental or commercial, may allocate their resources to address the current COVID-19 Pandemic or experience delays or disruptions in their ability to devote resources to coverage and reimbursement matters related to our products or medicines as a result of the COVID-19 Pandemic, which would negatively affect the potential commercial success of our products, our revenue and our profits.

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

To successfully commercialize any of our medicines, we would need to optimize and manage large-scale commercial manufacturing capabilities either on a standalone basis or through a third-party manufacturer. We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and drug product for WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities, including any interruption to our supply chain as a result of the current COVID-19 Pandemic, could limit the commercial success of our medicines. In addition, as our drug development and commercial pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. For example, we have plans to expand our manufacturing infrastructure to support our wholly owned pipeline. If we are not successful in executing this expansion, it could limit our ability to meet our manufacturing requirements and commercial objectives in the future.

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

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

Risks Related to the Development and Regulatory Approval of our Medicines

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

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

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

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

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

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

We may not be able to benefit from orphan drug designation for our medicines.

In the U.S., under the Orphan Drug Act, the FDA may designate a medicine as an orphan drug if it is intended to treat a rare disease or condition affecting fewer than 200,000 individuals in the U.S. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods. The FDA has granted orphan drug designation to eplontersen for the treatment of patients with transthyretin-mediated amyloidosis. The FDA and EMA have granted orphan drug designation to TEGSEDI for the treatment of patients with polyneuropathy due to hATTR amyloidosis, to WAYLIVRA for the treatment of patients with FCS, and to tominersen for the treatment of patients with HD. In addition, the EMA has granted orphan drug designation to WAYLIVRA for the treatment of patients with FPL. Even if approval is obtained on a medicine that has been designated as an orphan drug, we may lose orphan drug exclusivity if the FDA or EMA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable medicine to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain approval for the same medicine in a safer or more effective form or that makes a major contribution to patient care. If we lose orphan drug exclusivity on any of our medicines, we may face increased competition and lose market share for such medicine.

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

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

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. If any of our medicines in Phase 3 clinical studies, including the studies of eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen, do not show sufficient efficacy in patients with the targeted indication, or if such studies are discontinued for any other reason, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

In the past, we have invested in clinical studies of medicines that have not met the primary clinical endpoints in their Phase 3 studies or have been discontinued for other reasons. For example, in October 2021, Biogen reported that tofersen did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring tofersen were seen across multiple secondary and exploratory measures of disease activity and clinical function. In addition, in March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest Huntington's disease based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded Independent Data Monitoring Committee. Similar results could occur in clinical studies for our other medicines, including the studies of eplontersen, olezarsen, donidalorsen, ION363 and pelacarsen.

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

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

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

Any failure or delay in our clinical studies, including the studies of tofersen, pelacarsen, eplontersen, olezarsen, donidalorsen, and ION363, could reduce the commercial potential or viability of our medicines.

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

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our medicines and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, Syneos Health, Inc., PPD and Medpace for the clinical studies for our medicines, including eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that these third parties conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations, including as a result of delays or disruption caused by the current COVID-19 Pandemic that may affect the third party's ability to conduct the clinical studies for our medicines, or a termination of our relationship with these third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines or additional marketing authorizations for TEGSEDI and WAYLIVRA.

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

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

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

- AstraZeneca for the joint development and funding of eplontersen;
- Novartis for development and funding of pelacarsen;
- Biogen for development and funding of tofersen; and
- Roche for development and funding of tominersen.

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, after a review of data from the global Phase 2b study of vupanorsen, Pfizer decided to discontinue the clinical development program for vupanorsen.

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

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

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

For planning purposes, we estimate and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain medicine will enter clinical trials, when we anticipate completing a clinical study, or when we anticipate filing an application for, or obtaining, marketing authorization, or when we or our partners plan to commercially launch a medicine. We base our estimates on present facts and a variety of assumptions, many of which are outside of our control, including the current COVID-19 Pandemic. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen, the price of our securities could decrease.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition

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

Because drug discovery and development requires substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, 2021, we had an accumulated deficit of approximately $1.2 billion and stockholders' equity of approximately $0.8 billion. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from 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 medicines or achieve or sustain future profitability.

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

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our drug programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorizations, preclinical activities and commitment of significant additional resources prior to their successful commercialization. These activities will require significant cash. As of December 31, 2021, we had cash, cash equivalents and short-term investments equal to $2.1 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- successful commercialization of SPINRAZA, TEGSEDI and WAYLIVRA;
- additional marketing approvals for WAYLIVRA and TEGSEDI;
- the profile and launch timing of our medicines, including eplontersen, olezarsen, donidalorsen, ION363, pelacarsen and tofersen;
- 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;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- our manufacturing requirements and capacity to fulfill such requirements.

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

Risks related to our intellectual property

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

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

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

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

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

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

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

Risks related to our personnel

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

In January 2020, Dr. Crooke, our founder and Chief Executive Officer, transitioned from Chief Executive Officer to Executive Chairman of our Board of Directors, and Dr. Monia, who was our Chief Operating Officer and a member of our team since our founding over 30 years ago, began serving as our Chief Executive Officer. Following the 2021 Annual Meeting of Stockholders, Dr. Crooke stepped down from the Board and now serves as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities. In June 2021, Dr. Loscalzo, a member of our Board since February 2014, was appointed Chairman of the Board. 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.

Risks related to taxes

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

Under the Internal Revenue Code of 1986, as amended, or the Code, a corporation is generally allowed a deduction for net operating losses, or NOLs, carried over from a prior taxable year. Under the Code, 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 current U.S. federal income tax law, U.S. federal NOLs generated in taxable years beginning after December 31, 2017 may be carried forward indefinitely, but the deductibility of such U.S. federal NOLs in taxable years beginning after December 31, 2020 is limited to 80 percent of taxable income. It is uncertain if and to what extent various states will conform to current U.S. federal income tax law, and there may be periods during which states suspend or otherwise limit the use of NOLs for state income tax purposes.

In addition, under Sections 382 and 383 of the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50 percentage-point cumulative change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change NOL 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 NOL carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. As a result of the Akcea Merger, we are subject to the separate return limitation year, or SRLY, rules. Under the SRLY rules, our utilization of Akcea's pre-merger NOL and tax credit carryforwards is limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre-merger tax attributes cannot be used to offset any of the income that Ionis contributes to our consolidated taxable income. In addition, at the state level, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

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

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

We could be subject to additional tax liabilities.

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

General risk factors

If the price of our securities continues to be highly volatile, this could make it harder 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, 2021, the market price of our common stock ranged from $64.37 to $25.04 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, the commercial success of our approved medicines, governmental regulation, marketing authorizations, changes in payers' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines.

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

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

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

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

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

In April 2021, we completed a $632.5 million offering of 0% Notes and used a portion of the net proceeds from the issuance of the 0% Notes to repurchase $247.9 million of our 1% Notes for $257.0 million. In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes. Additionally, in connection with the pricing of our 0% Notes and 0.125% Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser.

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, we may issue approximately 17.5 million shares of our common stock upon conversion of our 0% Notes and 0.125% Notes, up to 10.9 million shares in connection with the warrant transactions we entered into in connection with the issuance of our 0% Notes, and up to 6.6 million shares in connection with the warrant transactions we entered into in connection with the issuance of our 0.125% Notes, in each case subject to customary anti-dilution adjustments. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

In addition, pursuant to the call spread transactions we entered into in connection with the pricing of our 0% Notes and 0.125% Notes, the counterparties are likely to modify their hedge positions from time to time at or prior to the conversion or maturity of the notes by purchasing and selling shares of our common stock, other of our securities, or other instruments, including over-the-counter derivative instruments, that they may wish to use in connection with such hedging, which may have a negative effect on the conversion value of those notes and an adverse impact on the trading price of our common stock. The call spread transactions are expected generally to reduce potential dilution to holders of our common stock upon any conversion of our 0% Notes or 0.125% Notes or offset any cash payments we are required to make in excess of the principal amount of the converted 0% Notes or 0.125% Notes, as the case may be. However, the warrant transactions could separately have a dilutive effect to the extent that the market value per share of our common stock exceeds the applicable strike price of the warrants.

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

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

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

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

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

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

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

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

Our business may be adversely affected by climate change, extreme weather events, earthquakes, pandemics, civil or political unrest, terrorism or other catastrophic events.

In recent years, extreme weather events and changing weather patterns have become more common. As a result, we are potentially exposed to varying natural disaster or extreme weather risks such as hurricanes, tornadoes, fires, droughts, floods, or other events that may result from the impact of climate change on the environment. The potential impacts of climate change may also include increased operating costs associated with additional regulatory requirements and investments in reducing energy, water use and greenhouse gas emissions. In addition, we manufacture most of our research and clinical supplies in a manufacturing facility located in Carlsbad, California. We manufacture the finished drug product for TEGSEDI and WAYLIVRA at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA. The facilities and the equipment we, our partners and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace. Our facilities or those of our partners or contract manufacturers may be harmed by natural disasters or other events outside our control, such as earthquakes, pandemics, war, civil or political unrest, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, and if such facilities are affected by a disaster or other event, our development and commercialization efforts would be delayed. Although we possess property damage and business interruption insurance coverage, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

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

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

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

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

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

A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business. In addition to our U.S. operations, we are commercializing TEGSEDI in the EU, Canada, Latin America and certain Caribbean countries, and WAYLIVRA in the EU, Latin America and certain Caribbean countries. We face risks associated with our international operations, including possible unfavorable regulatory, pricing and reimbursement, political, tax and labor conditions, which could harm our business. Because we have international operations, we are subject to numerous risks associated with international business activities, including:

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

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

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

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

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

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

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

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

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 16, 2022, the following are the primary facilities in which we operate:

Property Description	Location	Square Footage	Owned or Leased	Initial Lease Term End Date	Lease Extension Options
Laboratory and office space facility	Carlsbad, CA	176,000	Owned		
Office and meeting space facility	Carlsbad, CA	74,000	Owned		
Manufacturing facility	Carlsbad, CA	26,800	Owned		
Manufacturing support facility	Carlsbad, CA	25,800	Leased	2026	One, five-year option to extend
Office and storage space facility	Carlsbad, CA	18,700	Leased	2023	One, five-year option to extend
Office space facility	Boston, MA	14,300	Leased	2029	One, five-year option to extend
Office space facility	Carlsbad, CA	5,800	Leased	2023	One, five-year option to extend
		341,400			

We believe that our current and future facilities will be adequate for the foreseeable future.

Item 3. Legal Proceedings

For details of legal proceedings, see Note 10, *Legal Proceedings*, in the Notes to the Consolidated Financial Statements.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

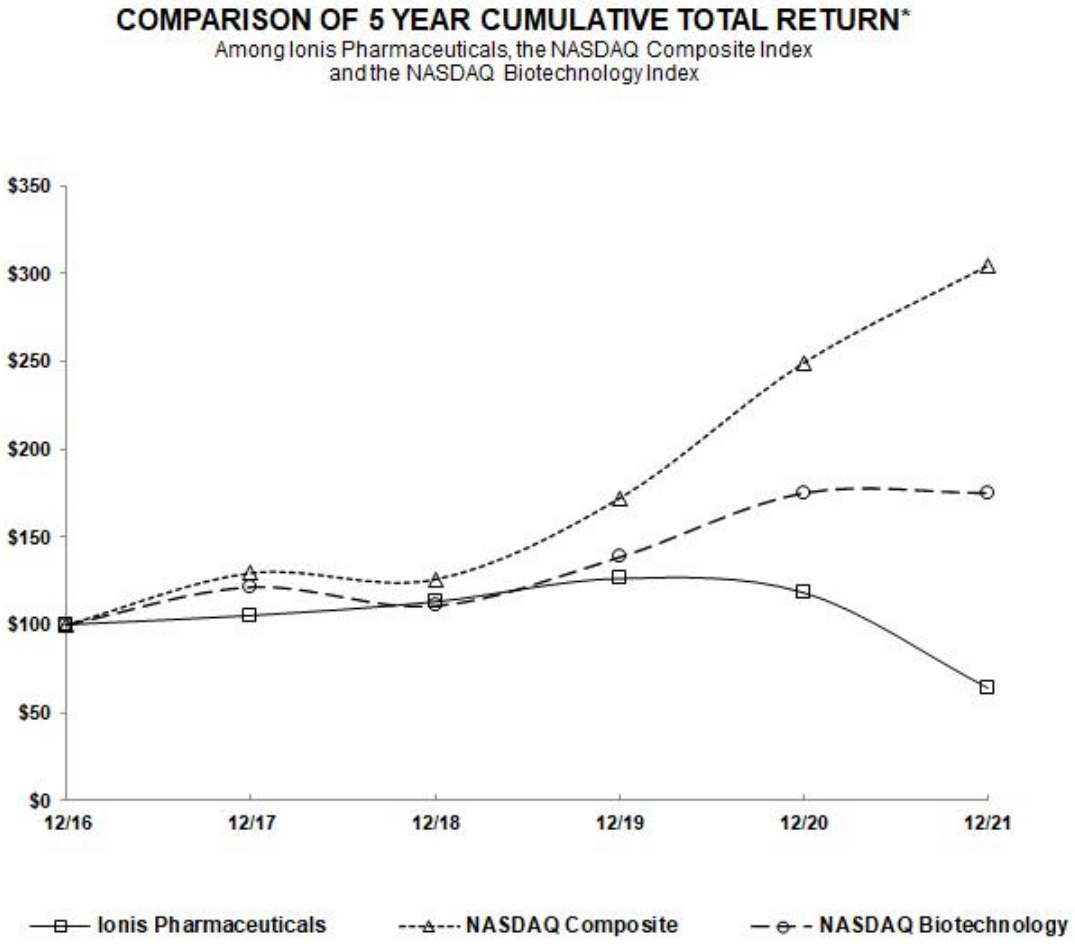
Market Information and Dividends

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "IONS." As of February 16, 2022, there were approximately 495 stockholders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of stockholders represented by these record holders.

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

Performance Graph (1)

Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2016 in our common stock, the Nasdaq Composite Index (total return) and the Nasdaq Biotechnology Index. The total return assumes reinvestment of dividends.



* $100 invested on December 31, 2016 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-16	Dec-17	Dec-18	Dec-19	Dec-20	Dec-21
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 105.16	$ 113.03	$ 126.30	$ 118.21	$ 63.62
Nasdaq Composite Index	$ 100.00	$ 129.64	$ 125.96	$ 172.17	$ 249.51	$ 304.85
Nasdaq Biotechnology Index	$ 100.00	$ 121.63	$ 110.85	$ 138.69	$ 175.33	$ 175.37

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

Item 6. Selected Financial Data

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

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

This financial review presents our operating results for each of the two years in the period ended December 31, 2021, and our financial condition at December 31, 2021. Refer to our 2020 Form 10-K for our results of operations for 2020 compared to 2019. Except for the historical information contained herein, the following discussion contains forward-looking statements that are subject to known and unknown risks, uncertainties and other factors that may cause our actual results to differ materially from those expressed or implied by such forward-looking statements. We discuss such risks, uncertainties and other factors throughout this report and specifically under Item 1A of Part I of this report, "Risk Factors." In addition, the following review should be read in conjunction with the information presented in our consolidated financial statements and the related notes to our consolidated financial statements as indexed on page F-1.

Overview

As noted in our Business Overview in Part I of this report, we are a leader in RNA-targeted therapeutics. We believe our medicines, which are based on our novel antisense technology, have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases. We currently have three marketed medicines- SPINRAZA, TEGSEDI and WAYLIVRA. We also have a rich late-stage pipeline of medicines, primarily focused on our cardiovascular and neurology franchises. Within our late-stage pipeline, we have six medicines in Phase 3 development for eight indications. For further details on our business refer to the Business section of Part I of this report.

Financial Highlights

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

	Year Ended December 31,	
	2021	2020 (as revised*)
Total revenue	$ 810.5	$ 729.3
Total operating expenses	$ 840.6	$ 901.3
Loss from operations	$ (30.2)	$ (172.1)
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (28.6)	$ (479.7)
Cash, cash equivalents and short-term investments	$ 2,115.0	$ 1,892.4

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

Our revenue for 2021 increased compared to 2020 due to significant partner payments across our cardiology and neurology franchises. Our commercial revenue for 2021 included SPINRAZA royalties, TEGSEDI and WAYLIVRA revenue and licensing and other royalty revenue. As a result of our distribution agreements with Sobi for TEGSEDI and WAYLIVRA, our commercial revenue from product sales shifted to revenue from distribution fees based on net sales generated by Sobi. We completed the transition of our TEGSEDI and WAYLIVRA commercial operations in Europe and our TEGSEDI commercial operations in North America to Sobi in the first and second quarters of 2021, respectively.

We earn our R&D revenue from multiple sources that can fluctuate depending on the timing of events. Our R&D revenue increased in 2021 compared to 2020 primarily due to the joint development and commercialization collaboration we entered into with AstraZeneca in 2021.

Our operating expenses, excluding $90 million of expenses related to the Akcea Merger and restructured European operations we incurred in 2020, increased in 2021 compared to 2020 due to an increase in R&D expenses, partially offset by a decrease in SG&A expenses. Higher R&D expenses were primarily driven by our ongoing investments in advancing our Phase 3 programs, expanding the number of Phase 3 studies and advancing and expanding our mid-stage pipeline. Additionally, we invested in our technology resulting in higher R&D expenses, which was primarily driven by the $35 million we paid in 2021 to license Bicycle's technology. As anticipated, our SG&A expenses were lower in 2021 compared to 2020 due to operating efficiencies we achieved from integrating Akcea and restructuring our commercial operations.

At December 31, 2021, we had $2.1 billion in cash and short-term investments, compared with $1.9 billion as of December 31, 2020, enabling us to accelerate investments in our strategic priorities, while maintaining a strong financial foundation.

Business Segment

In 2021, we began operating as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment. Previously, we had operated as two operating segments, Ionis Core and Akcea Therapeutics. We completed the Akcea Merger in October 2020 and fully integrated Akcea's operations into ours as of January 1, 2021.

Critical Accounting Estimates

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

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

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

In 2021, we determined the estimation of our income taxes was no longer a critical accounting estimate because we recorded a valuation allowance against the entirety of our net deferred tax assets in the fourth quarter of 2020.

The following are descriptions of our critical accounting estimates.

Revenue Recognition

We earn revenue from several sources. The judgements and estimates we make vary between each source of our revenue. At contract inception, we analyze our collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of ASC Topic 808, Collaborative Arrangements (ASC 808). For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration reflect a vendor-customer relationship and therefore within the scope of ASC 606. When we determine elements of a collaboration do not reflect a vendor-customer relationship, we consistently apply the reasonable and rational policy election we made by analogizing to authoritative accounting literature.

We evaluate the income statement classification for presentation of amounts due from or owed to other participants associated with multiple activities in a collaboration arrangement based on the nature of each separate activity. For example, in our eplontersen collaboration with AstraZeneca, we recognize funding received from AstraZeneca for co-development activities as revenue. While, we recognize cost sharing payments to and from AstraZeneca associated with co-commercialization activities and co-medical affairs activities as SG&A expense and research and development expense, respectively

The following is a summary of the critical accounting estimates we make with respect to each of our significant revenue sources.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

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

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

We recognize product sales in the period when our customer obtains control of our products. Prior to our distribution agreements with Sobi, we recorded TEGSEDI and WAYLIVRA commercial revenue at our net sales price, or transaction price, which included estimated reserves for discounts, returns, chargebacks, rebates and other allowances that we offered within contracts between us and our customers, wholesalers, distributors, health care providers and other indirect customers. Our reserves reflected our best estimates under the terms of our respective contracts. Our historical reserve estimates have not been materially different from our actual amounts. Under our agreements with Sobi, we transferred all reserves to Sobi and Sobi is responsible for any applicable reserves.

Research and development revenue under collaborative agreements

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

- Identifying the performance obligations contained in the agreement

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

- Determining the transaction price, including any variable consideration

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

  We are required to reassess the total transaction price at each reporting period to determine if we should include additional payments in the transaction price that have become probable. For example, in the fourth quarter of 2021, we achieved a milestone payment for $7.5 million under our 2018 strategic neurology collaboration with Biogen. Prior to achieving this milestone payment, we did not consider this payment probable. Upon achieving the milestone payment, we reassessed the total transaction price of our 2018 strategic neurology collaboration. We added this milestone payment to our total transaction price under our collaboration.

- Allocating the transaction price to each of our performance obligations

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

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

Amortization from Upfront Payments

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

Milestone Payments

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

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

License Fees

When we grant a license for a medicine in clinical development, we generally recognize as R&D revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner. For example, in 2021, we received a $200 million upfront payment when we entered into an agreement with AstraZeneca to jointly develop and commercialize eplontersen. Refer to Note 1, *Organization and Significant Accounting Policies*, for our revenue recognition policy. We discuss the estimates we make related to the relative stand-alone selling price of a license in detail above under "Allocating the transaction price to each of our performance obligations."

Estimated Liability for Clinical Development Costs

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

As of December 31, 2021, a hypothetical 10.0 percent increase in our liability for preclinical and clinical development costs would have resulted in an increase in our loss before income tax benefit and accrued liabilities by approximately $6.6 million.

Results of Operations

Below we have included our results of operations for 2021 compared to 2020. Refer to our 2020 Form 10-K for our results of operations for 2020 compared to 2019.

Years Ended December 31, 2021 and December 31, 2020

Revenue

Total revenue for 2021 was $810.5 million compared to $729.3 million in 2020 and was comprised of the following (amounts in millions):

	Year Ended December 31,	
	2021	**2020**
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 267.8	$ 286.6
TEGSEDI and WAYLIVRA revenue, net	55.5	70.0
Licensing and other royalty revenue	19.1	8.1
Total commercial revenue	342.4	364.7
R&D revenue:		
Amortization from upfront payments	77.5	79.6
Milestone payments	88.3	182.6
License fees	291.3	86.0
Other services	11.0	16.4
Total R&D revenue	468.1	364.6
Total revenue	$ 810.5	$ 729.3

Our revenue for 2021 increased compared to 2020 due to significant partner payments across our cardiology and neurology franchises. Our commercial revenue for 2021 included SPINRAZA royalties, TEGSEDI and WAYLIVRA revenue and licensing and other royalty revenue. As a result of our distribution agreements with Sobi for TEGSEDI and WAYLIVRA, our commercial revenue from product sales shifted to revenue from distribution fees based on net sales generated by Sobi. We completed the transition of our TEGSEDI and WAYLIVRA commercial operations in Europe and our TEGSEDI commercial operations in North America to Sobi in the first and second quarters of 2021, respectively.

We earn our R&D revenue from multiple sources that can fluctuate depending on the timing of events. Our R&D revenue increased in 2021 compared to 2020 primarily because we earned more revenue from license fees in 2021 than in 2020. Our R&D revenue in 2021 was comprised of $252 million from our cardiovascular franchise, including $200 million from AstraZeneca for its license of eplontersen and a $25 million milestone payment from Novartis when Novartis achieved 50 percent enrollment in the Phase 3 Lp(a) HORIZON study of pelacarsen. Additionally, our R&D revenue in 2021 included $168 million from our neurology franchise, with $60 million from Biogen for advancing ION306, our medicine in development for SMA based on new Ionis chemistry, and from advancing several other neurology targets.

Operating Expenses

Operating expenses for 2021 were $840.6 million, and decreased compared to $901.3 million for 2020. The decrease was principally due to $89.6 million of operating expenses related to the Akcea Merger and restructured European operations we incurred in 2020. Excluding expenses related to the Akcea Merger and restructured European operations, our operating expenses for 2021 increased compared to 2020 due to an increase in R&D expenses, partially offset by a decrease in SG&A expenses. Higher R&D expenses were primarily driven by our investments in advancing our Phase 3 programs. Additionally, we recognized $35 million in R&D expense in 2021 for licensing Bicycle's technology. Lower SG&A expenses primarily reflected operating efficiencies achieved from integrating Akcea and restructuring our commercial operations.

Our operating expenses were as follows (in millions):

	Year Ended December 31,	
	2021	2020
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 696.0	$ 640.9
Restructuring expenses	23.9	30.3
Total operating expenses, excluding non-cash compensation expense related to equity awards	719.9	671.2
Non-cash compensation expense related to equity awards	120.7	170.8
Restructuring expenses related to acceleration of Akcea's stock-based compensation expense due to Akcea Merger	—	59.3
Total operating expenses	$ 840.6	$ 901.3

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

Cost of Sales

Our cost of sales consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and WAYLIVRA and certain associated period costs.

Our cost of sales were as follows (in millions):

	Year Ended December 31,	
	2021	2020
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 10.4	$ 10.0
Non-cash compensation expense related to equity awards	0.4	1.9
Total cost of sales	$ 10.8	$ 11.9

Our cost of sales, excluding non-cash compensation expense related to equity awards, for 2021 were consistent with 2020.

Research, Development and Patent Expenses

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

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

	Year Ended December 31,	
	2021	2020
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 547.4	$ 411.3
Restructuring expenses	8.5	8.2
Total research, development and patent expenses, excluding non-cash compensation expense related to equity awards	555.9	419.5
Non-cash compensation expense related to equity awards	87.6	115.6
Total research, development and patent expenses	$ 643.5	$ 535.1

Antisense Drug Discovery

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

Our antisense drug discovery expenses were as follows (in millions):

	Year Ended December 31,	
	2021	2020
Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 136.6	$ 89.2
Non-cash compensation expense related to equity awards	21.4	24.2
Total antisense drug discovery expenses	$ 158.0	$ 113.4

Antisense drug discovery expenses, excluding non-cash compensation expense related to equity awards, increased in 2021 compared to 2020 primarily due to $35 million in R&D expense that we recognized in 2021 for licensing Bicycle's technology as discussed above.

Antisense Drug Development

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

	Year Ended December 31,	
	2021	2020
TEGSEDI and WAYLIVRA	$ 11.4	$ 20.3
Eplontersen	79.1	34.0
Olezarsen	22.0	5.6
Donidalorsen	6.7	6.4
ION363	7.7	2.6
Other antisense development projects	104.5	69.9
Development overhead expenses	83.7	85.9
Restructuring expenses	7.7	8.0
Total antisense drug development, excluding non-cash compensation expense related to equity awards	322.8	232.7
Non-cash compensation expense related to equity awards	39.2	63.7
Total antisense drug development expenses	$ 362.0	$ 296.4

Our development expenses, excluding non-cash compensation expense related to equity awards, increased in 2021 compared to 2020 primarily due to our numerous ongoing Phase 3 programs in addition to our advancing and expanding mid-stage pipeline.

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

Manufacturing and Development Chemistry

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

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

	Year Ended December 31,	
	2021	2020
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 47.2	$ 55.7
Restructuring expenses	0.8	0.2
Total manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	48.0	55.9
Non-cash compensation expense related to equity awards	11.5	10.9
Total manufacturing and development chemistry expenses	$ 59.5	$ 66.8

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, decreased in 2021 compared to 2020 due to costs we incurred to manufacture API for olezarsen and eplontersen in 2020.

R&D Support

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

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

	Year Ended December 31,	
	2021	2020
Personnel costs	$ 17.7	$ 14.7
Occupancy	13.1	10.2
Patent expenses	5.3	4.1
Insurance	3.2	2.4
Computer software and licenses	1.8	2.9
Other	7.3	7.4
Restructuring expenses	0.1	—
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	48.5	41.7
Non-cash compensation expense related to equity awards	15.5	16.8
Total R&D support expenses	$ 64.0	$ 58.5

R&D support expenses, excluding non-cash compensation expense related to equity awards, increased in 2021 compared to 2020. The increase was primarily related to increased personnel and occupancy costs to support advancing our pipeline and our technology.

Selling, General and Administrative Expenses

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

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

	Year Ended December 31,	
	2021	2020
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 138.1	$ 219.7
Restructuring expenses	15.4	22.1
Total selling, general and administrative expenses, excluding non-cash compensation related to equity awards	153.5	241.8
Non-cash compensation expense related to equity awards	32.8	112.5
Total selling, general and administrative expenses	$ 186.3	$ 354.3

SG&A expenses, excluding non-cash compensation expense related to equity awards, decreased in 2021 compared to 2020 due to operating efficiencies achieved from the Akcea Merger and restructuring our commercial operations. Non-cash compensation expense related to equity awards decreased in 2021 compared to 2020 due to reduced headcount as a result of the Akcea Merger and restructuring our commercial operations. In addition, our SG&A expenses in 2020 included non-cash stock-based compensation expense of $42.0 million related to the Akcea Merger and restructured European operations.

Investment Income

Investment income for 2021 was $10.0 million compared to $30.6 million for 2020. The decrease in investment income was primarily due to a decrease in interest rates during 2021 compared to 2020.

Interest Expense

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

	Year Ended December 31,	
	2021	2020 (as revised*)
Convertible senior notes:		
Non-cash amortization of the debt discounts and debt issuance costs	$ 4.9	$ 3.2
Interest expense payable in cash	1.9	3.8
Interest on mortgage for primary R&D and manufacturing facilities	2.4	2.4
Other	0.1	0.1
Total interest expense	$ 9.3	$ 9.5

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

Gain on Investments

Gain on investments for 2021 was $10.1 million compared to $16.5 million for 2020. During 2021, we revalued our investments in Bicycle and ProQR because we recognize publicly traded equity securities at fair value and recognized gains of $7.1 million and $1.8 million on our investments, respectively. During 2020, we revalued our investments in three privately held companies, Dynacure, Suzhou-Ribo and Aro Biotherapeutics because the companies sold additional equity securities that were similar to the equity we own. As a result of these observable price changes in 2020, we recognized a total gain of $14.8 million on our investments in these companies during 2020 because the sales were at higher prices compared to our recorded value.

Early Retirement of Debt

As a result of the debt offering and debt repurchase completed in April 2021, we recorded an $8.6 million loss on early retirement of debt, reflecting the early retirement of a portion of our 1% Notes. The loss on the early retirement of our debt is the difference between the amount we paid to retire our 1% Notes and the net carrying balance of the liability at the time that we retired the debt.

Income Tax Expense (Benefit)

We recorded an income tax benefit of $0.6 million for 2021 compared to an income tax expense of $345.2 million for 2020. Our 2020 income tax expense included a non-cash tax expense of $341 million related to an increase in the valuation allowance recorded against Ionis' U.S. federal net deferred tax assets in 2020. We now maintain a valuation allowance against all our consolidated U.S. federal and state net deferred tax assets. Refer to Note 5, *Income Taxes*, in the Notes to our consolidated financial statements for further details on our valuation allowance.

Net Loss

We generated a net loss of $28.6 million for 2021 compared to $479.7 million for 2020. Our net loss decreased for 2021 compared to 2020 primarily due to the valuation allowance we recorded in 2020 as a result of the Akcea Merger, as discussed above in the income tax expense (benefit) section. In addition, our revenue increased and expenses decreased year-over-year, as discussed above in the revenue and expenses sections, respectively.

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

Our noncontrolling interest in Akcea on our statement of operations for 2020 was a net loss of $35.5 million. This amount represents the portion of Akcea's net loss that third parties owned for the period from January 1, 2020 until we acquired 100 percent of Akcea in October 2020. After we completed the Akcea Merger in October 2020, we no longer recorded any adjustment related to noncontrolling interest for Akcea's net loss.

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

We had a net loss attributable to our common stockholders of $28.6 million for 2021 compared to $444.3 million in 2020. Basic and diluted net loss per share for 2021 were each $0.20. Basic and diluted net loss per share for 2020 were each $3.18.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also finance our operations from commercial revenue from SPINRAZA royalties and TEGSEDI and WAYLIVRA commercial revenue. From our inception through December 31, 2021, we have earned approximately $5.8 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through December 31, 2021, we have raised net proceeds of approximately $2.0 billion from the sale of our equity securities. Additionally, we borrowed approximately $2.1 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

Our cash, cash equivalents and short-term investments, debt obligations and working capital increased from 2020 to 2021, primarily as a result of receiving more than $760 million in payments from partners in 2021 and issuing $632.5 million of 0% Notes (due in April 2026). This increase was partially offset by our repurchase of $247.9 million of our 1% Notes in April 2021 and payment of the remaining principal balance of our 1% Notes with $62.0 million of cash at maturity in November 2021. At December 31, 2021, we had $2.1 billion of cash and short-term investments on hand. We believe our cash and short-term investment balance is sufficient to fund our operations in the short-term and in the longer-term. In 2021 our working capital increased because our cash and investments increased as discussed above.

The following table summarizes our contractual obligations as of December 31, 2021. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in Note 3, *Long-Term Obligations and Commitments*.

Contractual Obligations	**Payments Due by Period (in millions)**		
(selected balances described below)	**Total**	**Less than 1 year**	**More than 1 year**
0% Notes (principal payable)	$ 632.5	$ —	$ 632.5
0.125% Notes (principal and interest payable)	550.9	0.7	550.2
Building mortgage payments (principal and interest payable)	73.4	2.7	70.7
Operating leases	27.5	4.1	23.4
Other obligations (principal and interest payable)	0.8	0.1	0.7
Total	$ 1,285.1	$ 7.6	$ 1,277.5

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

Convertible Debt and Call Spread

Refer to our Convertible Debt and Call Spread accounting policies in Note 1, *Organization and Significant Accounting Policies*, and Note 3, *Long-Term Obligations and Commitments*, in the Notes to our consolidated financial statements for the significant terms of each convertible debt instrument.

Research and Development and Manufacturing Facilities

Refer to Note 3, *Long-Term Obligations and Commitments*, in the Notes to our consolidated financial statements for further details on our research and development and manufacturing facilities.

Operating Leases

Refer to Note 3, *Long-Term Obligations and Commitments*, in the Notes to our consolidated financial statements for further details on our operating leases.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2021 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to changes in interest rates primarily from our investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we were 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 as of December 31, 2021 and will not be subject to any material risks arising from these changes in the foreseeable future.

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, 2021.

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, 2021, 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, 2021.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2021, 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, 2021, 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, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2021 and 2020, 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, 2021, and the related notes and our report dated February 24, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

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

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

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

Definition and Limitations of Internal Control Over Financial Reporting

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

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

/s/ Ernst & Young LLP

San Diego, California
February 24, 2022

Item 9B. Other Information

Not applicable.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

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, 2021, or the Proxy Statement.

We include information concerning our executive officers in the section titled, *Information about our Executive Officers*, in this report on the Form 10-K in Item 1 titled "Business."

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

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

Delinquent Section 16(a) Reports

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

Item 11. Executive Compensation

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

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

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

Securities Authorized for Issuance under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2021.

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)	14,088,816	$ 54.04	11,102,267(b)
Total	14,088,816	$ 54.04	11,102,267

(a) Consists of five Ionis plans: 1989 Stock Option Plan, Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, 2011 Equity Incentive Plan, 2020 Equity Incentive Plan and Employee Stock Purchase Plan, or ESPP.
(b) Of these shares, 588,529 were available for purchase under the ESPP as of December 31, 2021.

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 Accountant Fees and Services

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

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

INDEX TO EXHIBITS

Exhibit Number	Description of Document
2.1	Agreement and Plan of Merger, dated as of August 30, 2020, among Akcea Therapeutics, Inc., Ionis Pharmaceuticals, Inc. and Avalanche Merger Sub, Inc., filed as an exhibit to the Registrant's Current Report on Form 8-K filed August 31, 2020 and incorporated herein by reference.
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
3.2	Certificate of Amendment to Restated Certificate of Incorporation, filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed on April 25, 2014 and incorporated herein by reference.
3.3	Certificate of Amendment to Restated Certificate of Incorporation, 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 March 29, 2021 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 Current Report on Form 8-K filed December 13, 2000 and incorporated herein by reference.
4.2	Specimen Common Stock Certificate, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
4.3	Indenture, dated as of November 17, 2014, between the Registrant and Wells Fargo Bank, National Association, as trustee, including Form of 1.00 percent Convertible Senior Note due 2021, filed as an exhibit to the Registrant's Current Report on Form 8-K filed November 21, 2014 and incorporated herein by reference.
4.4	Indenture, dated as of December 19, 2019, by and between the Registrant and U.S. Bank National Association, as trustee, including Form of 0.125 percent Convertible Senior Note due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 23, 2019 and incorporated herein by reference.
4.5	Indenture, dated as of April 12, 2021, by and between the Registrant and U.S. Bank National Association, as trustee, including Form of 0 percent Convertible Senior Note due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.
4.6	Form of Exchange and/or Subscription Agreement for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.7	Form of Convertible Note Hedge Transactions Confirmation for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.8	Form of Convertible Note Hedge Confirmation for Convertible Senior Notes due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.
4.9	Form of Warrant Transactions Confirmation for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.10	Form of Warrant Confirmation for Convertible Senior Notes due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.
4.11	Description of the Registrant's Securities.
10.1	Amended Board Compensation Policy, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2021 and incorporated herein by reference.

10.2	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.
10.3*	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 on April 16, 2012 and incorporated herein by reference.
10.4*	Registrant's Amended and Restated 2000 Employee Stock Purchase Plan, filed as an exhibit to Registrant's Current Report on Form 8-K filed on March 26, 2019 and incorporated herein by reference.
10.5	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.
10.6	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	Strategic Collaboration, Option and License Agreement by and among Akcea Therapeutics, Inc. and Novartis Pharma AG, dated January 5, 2017, filed as an exhibit to Akcea Therapeutics, Inc.'s Form S-1 filed March 27, 2017 and incorporated herein by reference.
10.9	Amendment No. 1 to the Strategic Collaboration, Option and License Agreement between Akcea Therapeutics, Inc. and Novartis Pharma AG dated February 22, 2019, filed as an exhibit to Akcea Therapeutics, Inc.'s Quarterly Report on Form 10-Q for the quarter ended March 30, 2019 and incorporated herein by reference.
10.10	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.
10.11	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.
10.12	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.
10.13*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended, filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement for the 2020 Annual Meeting of Stockholders, filed on April 24, 2020 and incorporated herein by reference.
10.14*	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 Registration Statement on Form S-8 filed on August 7, 2020 and incorporated herein by reference.
10.15	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.
10.16*	Amended and Restated Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Notice of 2021 Annual Meeting of Stockholders and Proxy Statement filed on April 23, 2021 and incorporated herein by reference.

10.17*	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.
10.18*	Form of Time-Vested Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on August 8, 2011 and incorporated herein by reference.
10.19*	Forms of Performance Based Restricted Stock Unit Grant Notice and Performance Based Restricted Stock Unit Agreement for Performance Based Restricted Stock Units granted under the 2011 Equity Incentive Plan.
10.20*	Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.21*	Form of Global Option Agreement for options granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.22*	Form of Global Restricted Stock Unit Agreement for restricted stock units granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.23*	Forms of Restricted Stock Unit Grant Notice, Stock Option Grant Notice and Stock Option Exercise Notice for options granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.24	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.
10.25*	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.
10.26*	Form of Option Agreement for Options granted under the 2002 Non-Employee Director's Stock Option Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on August 7, 2020 and incorporated herein by reference.
10.27	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.
10.28	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.
10.29	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.
10.30	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.
10.31	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.
10.32	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.

10.33	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.
10.34	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.
10.35	Amended and Restated Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated July 12, 2021, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.36	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.
10.37	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.
10.38	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.
10.39	Amendment No. 3 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated July 10, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.40	Amendment #4 to the Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated April 10, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.41	Amendment #5 to the Research, Development and License Agreement among the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.42	Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.43	Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.44	Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.45	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, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.46	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.
10.47	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.
10.48	Amendment #6 to Research, Development and License Agreement between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated September 2, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.49	Amendment 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.
10.50	License Agreement between the Registrant and Bayer Pharma AG dated May 1, 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. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.51	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.
10.52	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.
10.53	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.
10.54	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.
10.55	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, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.56	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.

10.57	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.
10.58	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.
10.59*	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.
10.60	Fourth Amended and Restated Strategic Advisory Services Agreement by and between the Registrant and B. Lynne Parshall, dated February 22, 2022.
10.61	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.
10.62	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.
10.63	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.
10.64	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.
10.65	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.
10.66	Factor B Development Collaboration, Option and License Agreement by and between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., dated October 9, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.67	Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated October 17, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.68	Amendment #1 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.69	Amendment #4 to the Collaboration, License and Development Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.70	Amendment #1 to Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated May 2, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2019 and incorporated herein by reference.

10.71	Amendment #1 to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc., dated August 16, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.72	Amendment #8 to the Research, Development and License Agreement between the Registrant, Glaxo Group Limited and Glaxosmithkline Intellectual Property Development Limited, dated July 29, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.73	Consent to Collateral Addition and Amendment to Loan Documents between the Registrant, Ionis Gazelle, LLC, Wells Fargo Bank, National Association, as Trustee for the Benefit of the Registered Holders of UBS Commercial Mortgage Trust 2017-C3, Commercial Mortgage Pass-Through Certificates, Series 2017-C3, dated August 1, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference.
10.74	License Agreement by and among Akcea Therapeutics, Inc. and Pfizer Inc. dated October 4, 2019, filed as an exhibit to Akcea Therapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2019 and incorporated herein by reference.
10.75	Letter Agreement between the Registrant, Akcea Therapeutics, Inc., and Pfizer Inc., dated October 4, 2019, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.76	Side Letter dated June 11, 2020 to the Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated October 17, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.77	Amendment No. 2 dated April 30, 2020 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.78	Letter agreement dated October 21, 2020 to the License Agreement by and among Akcea Therapeutics, Inc. and Pfizer Inc. dated October 4, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.79	Amendment No. 3 dated December 17, 2020 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.80	Strategic Advisory Services Agreement by and between the Registrant and Stanley T. Crooke, dated December 17, 2020, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2020 and incorporated herein by reference.
10.81	Side Letter dated December 31, 2020 to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated April 19, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.

10.82	Collaboration and License Agreement by and between the Registrant and BicycleTX Limited dated July 9, 2021, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.83	Amendment No. 1 dated December 17, 2021 to the Collaboration and License Agreement by and between the Registrant and BicycleTX Limited dated July 9, 2021. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
10.84	Collaboration and License Agreement by and between Akcea Therapeutics, Inc. and AstraZeneca AB dated December 6, 2021. Portions of this exhibit have been omitted because they are both (i) not material and (ii) would be competitively harmful if publicly disclosed.
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney – Included on the signature page of this Annual Report on Form 10-K.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1+	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2021, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of comprehensive income (loss), (iv) consolidated statements of stockholders' equity (v) consolidated statements of cash flows, and (vi) notes to consolidated financial statements (detail tagged).
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101).

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

\+ This certification is deemed not filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 133, as amended, or the Securities Exchange Act of 1934, as amended.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 24th day of February, 2022.

IONIS PHARMACEUTICALS, INC.

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

POWER OF ATTORNEY

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

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

Signatures	Title	Date
/s/ BRETT P. MONIA Brett P. Monia, Ph.D.	Director and Chief Executive Officer (Principal executive officer)	February 24, 2022
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 24, 2022
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Chairman of the Board	February 24, 2022
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 24, 2022
/s/ ALLENE M. DIAZ Allene M. Diaz	Director	February 24, 2022
/s/ MICHAEL HAYDEN Michael Hayden, CM OBC MB ChB PhD FRCP(C) FRSC	Director	February 24, 2022
/s/ JOAN E. HERMAN Joan E. Herman	Director	February 24, 2022
/s/ JOSEPH KLEIN Joseph Klein, III	Director	February 24, 2022
/s/ FREDERICK T. MUTO Frederick T. Muto, Esq.	Director	February 24, 2022
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director and Senior Strategic Advisor	February 24, 2022
/s/ JOSEPH H. WENDER Joseph H. Wender	Lead Independent Director	February 24, 2022

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, 2021 and 2020, 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, 2021, 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, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, 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, 2021, based on criteria established in Internal Control — Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 24, 2022 expressed an unqualified opinion thereon.

Adoption of ASU No. 2020-06

As discussed in Note 1 to the consolidated financial statements, the Company changed its method of accounting for convertible instruments for all years presented, 2019 through 2021, due to the adoption of ASU No. 2020-06, *Debt–Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging–Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity*.

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.

Critical Audit Matters

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

AstraZeneca – Eplontersen Collaboration

Description of the Matter

As discussed in Note 6 to the consolidated financial statements, the Company entered into a joint development and commercialization agreement with AstraZeneca AB ("AstraZeneca"), referred to as the "AstraZeneca agreement", which resulted in the recognition of $200 million in revenue for the year ended December 31, 2021. The Company determined that there were four material components of the AstraZeneca agreement: (i) license granted to AstraZeneca to develop and commercialize eplontersen; (ii) the parties' co-development activities for eplontersen; (iii) the parties' co-commercialization activities for eplontersen; and (iv) the parties' co-medical affairs activities for eplontersen.

Auditing management's initial application of the relevant US GAAP guidance under Accounting Standards Codification (ASC) 606, Revenue from Contracts With Customers, and ASC 808, Collaborative Arrangements, related to the AstraZeneca Agreement was especially challenging due to the complex nature of its terms and conditions. In particular, determining the distinct performance obligations with a customer was highly judgmental.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design and tested the operating effectiveness of internal controls over management's review of the terms and conditions of the AstraZeneca Agreement, identification of performance obligations, and consideration of the appropriate accounting guidance in determining the appropriate conclusions.

To test management's initial application of the accounting guidance to the AstraZeneca Agreement, we performed audit procedures that included, among others, reading the contractual agreement and assessing management's application of the appropriate accounting guidance in their evaluation. Our procedures included evaluating management's identification of distinct performance obligations with a customer. We also evaluated alternative views and any contrary or corroborative evidence associated with management's evaluation, and discussed with management the underlying business objectives of the AstraZeneca Agreement.

Estimated Liability for Clinical Development Costs

Description of the Matter

As of December 31, 2021, the Company accrued $65.7 million for accrued clinical development costs. As discussed in Note 2 to the consolidated financial statements, the Company records costs for clinical trial activities based upon estimates of costs incurred through the balance sheet date that have yet to be invoiced related to clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants.

Auditing the Company's accruals for clinical development costs is especially complex as the information necessary to estimate the accruals is accumulated from multiple sources. In addition, in certain circumstances, the determination of the nature and level of services that have been received during the reporting period requires judgment because the timing and pattern of vendor invoicing does not correspond to the level of services provided and there may be delays in invoicing from vendors.

How We Addressed the Matter in Our Audit

We obtained an understanding and evaluated the design and tested the operating effectiveness of controls over the accounting for accrued clinical development costs. This included controls over management's assessment of the assumptions and accuracy of data underlying the accrued clinical development expenses estimate.

To test the accuracy of the Company's accrued clinical development costs, we performed audit procedures that included, among other procedures, obtaining supporting evidence of the research and development activities performed for significant clinical trials. We corroborated the status of significant clinical development costs through meetings with accounting and clinical project managers. We compared the costs for a sample of transactions against the related invoices and contracts, and examined a sample of subsequent payments to evaluate the accuracy of the accrued clinical development costs and compared the results to the current year accrual.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 1989.

San Diego, California
February 24, 2022

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

	December 31,	
	2021	**2020**
		(as revised*)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 869,191	$ 397,664
Short-term investments	1,245,782	1,494,711
Contracts receivable	61,896	76,204
Inventories	24,806	21,965
Other current assets	143,374	140,163
Total current assets	2,345,049	2,130,707
Property, plant and equipment, net	178,069	181,077
Patents, net	29,005	27,937
Deposits and other assets	59,567	50,034
Total assets	$ 2,611,690	$ 2,389,755
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 11,904	$ 17,199
Accrued compensation	38,810	65,728
Accrued liabilities	88,560	90,161
Income taxes payable	36	1,324
1 percent convertible senior notes, net	—	308,809
Current portion of long-term obligations	3,526	7,301
Current portion of deferred contract revenue	97,714	108,376
Total current liabilities	240,550	598,898
Long-term deferred contract revenue	351,879	424,046
0 percent convertible senior notes, net	619,119	—
0.125 percent convertible senior notes, net	542,314	540,136
Long-term obligations, less current portion	26,378	23,409
Long-term mortgage debt	59,713	59,984
Total liabilities	1,839,953	1,646,473
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 141,210,015 and 140,365,594 shares issued and outstanding at December 31, 2021 and December 31, 2020, respectively	141	140
Additional paid-in capital	1,964,167	1,895,519
Accumulated other comprehensive loss	(32,668)	(21,071)
Accumulated deficit	(1,159,903)	(1,131,306)
Total stockholders' equity	771,737	743,282
Total liabilities and stockholders' equity	$ 2,611,690	$ 2,389,755

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. 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)

	Year Ended December 31,		
	2021	**2020**	**2019**
		(as revised*)	**(as revised*)**
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 267,776	$ 286,583	$ 292,992
TEGSEDI and WAYLIVRA revenue, net	55,500	69,999	42,253
Licensing and other royalty revenue	19,119	8,117	17,205
Total commercial revenue	342,395	364,699	352,450
Research and development revenue under collaborative agreements	468,061	364,565	770,149
Total revenue	810,456	729,264	1,122,599
Expenses:			
Cost of sales	10,842	11,947	4,384
Research, development and patent	643,453	535,077	465,688
Selling, general and administrative	186,347	354,322	286,644
Total operating expenses	840,642	901,346	756,716
Income (loss) from operations	(30,186)	(172,082)	365,883
Other income (expense):			
Investment income	10,044	30,562	52,013
Interest expense	(9,349)	(9,510)	(12,440)
Gain on investments	10,103	16,540	192
Loss on early retirement of debt	(8,627)	—	(66,196)
Other expenses	(1,133)	(62)	(686)
Income (loss) before income tax benefit (expense)	(29,148)	(134,552)	338,766
Income tax benefit (expense)	551	(345,191)	(51,507)
Net income (loss)	(28,597)	(479,743)	287,259
Net (income) loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	—	35,480	(9,116)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (28,597)	$ (444,263)	$ 278,143
Basic net income (loss) per share	$ (0.20)	$ (3.18)	$ 2.00
Shares used in computing basic net income (loss) per share	141,021	139,612	139,998
Diluted net income (loss) per share	$ (0.20)	$ (3.18)	$ 1.90
Shares used in computing diluted net income (loss) per share	141,021	139,612	153,164

* We revised our 2020 and 2019 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. 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)

	Year Ended December 31,		
	2021	2020 (as revised*)	2019 (as revised*)
Net income (loss)	$ (28,597)	$ (479,743)	$ 287,259
Unrealized gains (losses) on investments, net of tax	(11,486)	3,729	6,633
Currency translation adjustment	(111)	617	93
Adjustments to other comprehensive loss from purchase of noncontrolling interest of Akcea Therapeutics, Inc.	—	(127)	—
Comprehensive income (loss)	(40,194)	(475,524)	293,985
Comprehensive income (loss) attributable to noncontrolling interest in Akcea Therapeutics, Inc.	—	(35,480)	9,116
Comprehensive income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (40,194)	$ (440,044)	$ 284,869

* We revised our 2020 and 2019 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. 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, 2021, 2020 and 2019
(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, 2018 (as revised*)	137,929	$ 138	$ 1,833,668	$ (32,016)	$ (840,251)	$ 961,539	$ 139,084	$ 1,100,623
Net income	—	—	—	—	278,143	278,143	—	278,143
Change in unrealized losses, net of tax	—	—	—	6,633	—	6,633	—	6,633
Foreign currency translation	—	—	—	93	—	93	—	93
Issuance of common stock in connection with employee stock plans	3,100	3	119,654	—	—	119,657	—	119,657
Issuance of warrants	—	—	56,110	—	—	56,110	—	56,110
Purchase of note hedges, net of tax	—	—	(85,860)	—	—	(85,860)	—	(85,860)
Repurchases and retirements of common stock	(535)	(1)	—	—	(34,387)	(34,388)	—	(34,388)
Stock-based compensation expense	—	—	146,574	—	—	146,574	—	146,574
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(154)	—	(19,242)	—	—	(19,242)	—	(19,242)
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(65,254)	—	—	(65,254)	74,370	9,116
Balance at December 31, 2019 (as revised*)	140,340	$ 140	$ 1,985,650	$ (25,290)	$ (596,495)	$ 1,364,005	$ 213,454	$ 1,577,459
Net loss	—	—	—	—	(444,263)	(444,263)	—	(444,263)
Change in unrealized gain, net of tax	—	—	—	3,729	—	3,729	—	3,729
Foreign currency translation	—	—	—	617	—	617	—	617
Issuance of common stock in connection with employee stock plans	1,721	1	52,033	—	—	52,034	—	52,034
Purchase of noncontrolling interest of Akcea Therapeutics, Inc., including cash payments for cancellation of Akcea Therapeutics, Inc. equity awards	—	—	(324,022)	301	—	(323,721)	(220,965)	(544,686)
Repurchases and retirements of	(1,478)	(1)	—	—	(90,548)	(90,549)	—	(90,549)

common stock								
Stock-based compensation expense	—	—	230,117	—	—	230,117	—	230,117
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(217)	—	(13,410)	—	—	(13,410)	—	(13,410)
Deferred tax liability adjustment due to purchase of noncontrolling interest of Akcea Therapeutics, Inc.	—	—	7,714	—	—	7,714	—	7,714
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(42,563)	(428)	—	(42,991)	7,511	(35,480)
Balance at December 31, 2020 (as revised*)	140,366	$ 140	$ 1,895,519	$ (21,071)	$ (1,131,306)	$ 743,282	$ —	$ 743,282
Net loss	—	—	—	—	(28,597)	(28,597)	—	(28,597)
Change in unrealized gains, net of tax	—	—	—	(11,486)	—	(11,486)	—	(11,486)
Foreign currency translation	—	—	—	(111)	—	(111)	—	(111)
Issuance of common stock in connection with employee stock plans	1,132	1	11,563	—	—	11,564	—	11,564
Issuance of warrants	—	—	89,752	—	—	89,752	—	89,752
Purchases of note hedges	—	—	(136,620)	—	—	(136,620)	—	(136,620)
Stock-based compensation expense	—	—	120,678	—	—	120,678	—	120,678
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(288)	—	(16,725)	—	—	(16,725)	—	(16,725)
Balance at December 31, 2021	141,210	$ 141	$ 1,964,167	$ (32,668)	$ (1,159,903)	$ 771,737	$ —	$ 771,737

* We revised our 2018, 2019 and 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. 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)

	Year Ended December 31,		
	2021	2020 (as revised*)	2019 (as revised*)
Operating activities:			
Net income (loss)	$ (28,597)	$ (479,743)	$ 287,259
Adjustments to reconcile net income (loss) to net cash provided by operating activities:			
Depreciation	15,487	13,365	12,540
Amortization of right-of-use operating lease assets	1,721	1,731	1,542
Amortization of patents	2,352	2,064	1,912
Amortization of premium (discount) on investments, net	17,776	11,521	(7,485)
Amortization of debt issuance costs	4,958	3,255	2,945
Stock-based compensation expense	120,678	230,117	146,574
Loss on early retirement of debt	8,627	—	66,196
Gain on investments	(1,092)	(16,540)	(192)
Deferred income taxes, including changes in valuation allowance	—	341,729	911
Non-cash losses related to patents	2,707	1,948	2,226
Changes in operating assets and liabilities:			
Contracts receivable	14,308	(13,170)	(47,674)
Inventories	(2,841)	(1,261)	(5,411)
Other current and long-term assets	(877)	(9,975)	(44,659)
Long-term income taxes receivable (payable)	1,008	(89)	8,418
Accounts payable	(6,000)	(2,755)	(16,343)
Income taxes	(1,288)	(31,190)	31,656
Accrued compensation	(26,918)	28,371	8,089
Accrued liabilities and other current liabilities	(8,381)	32,424	16,406
Deferred contract revenue	(82,829)	(75,910)	(119,283)
Net cash provided by operating activities	30,799	35,892	345,627
Investing activities:			
Purchases of short-term investments	(1,124,193)	(1,570,410)	(1,946,726)
Proceeds from the sale of short-term investments	1,344,185	1,885,935	1,951,734
Purchases of property, plant and equipment	(11,955)	(35,120)	(30,905)
Acquisition of licenses and other assets, net	(5,946)	(5,928)	(5,377)
Purchases of strategic investments	(7,185)	—	(10,000)
Net cash provided by (used in) investing activities	194,906	274,477	(41,274)
Financing activities:			
Proceeds from equity, net	11,565	52,036	119,657
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(16,725)	(13,411)	(19,242)
Proceeds from the issuance of 0 percent convertible senior notes	632,500	—	—
Proceeds from the issuance of 0.125 percent convertible senior notes	—	—	109,500
0 percent convertible senior notes issuance costs	(15,609)	—	—
0.125 percent convertible senior notes issuance costs	—	—	(10,428)
Repurchase of $247.9 million principal amount of 1 percent convertible senior notes	(256,963)	—	—
Repayment of remaining principal amount of 1 percent convertible senior notes at maturity	(61,967)	—	—
Proceeds from issuance of warrants	89,752	—	56,110
Purchase of note hedges	(136,620)	—	(108,684)
Repurchases and retirements of common stock	—	(90,548)	(34,392)
Purchase of noncontrolling interest of Akcea Therapeutics, Inc., including cash payments for cancellation of Akcea Therapeutics, Inc. equity awards	—	(544,686)	—
Principal payments on line of credit	—	—	(12,500)
Net cash provided by (used in) financing activities	245,933	(596,609)	100,021
Effects of exchange rates on cash	(111)	617	93
Net increase (decrease) in cash and cash equivalents	471,527	(285,623)	404,467
Cash and cash equivalents at beginning of year	397,664	683,287	278,820
Cash and cash equivalents at end of year	$ 869,191	$ 397,664	$ 683,287

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

	Year Ended December 31,		
	2021	**2020**	**2019**
Supplemental disclosures of cash flow information:			
Interest paid	$ 4,778	$ 6,247	$ 9,870
Income taxes paid	$ 38	$ 25,855	$ 9,041
Supplemental disclosures of non-cash investing and financing activities:			
Right-of-use assets obtained in exchange for lease liabilities	$ 6,641	$ 2,149	$ 14,178
Amounts accrued for capital and patent expenditures	$ 705	$ 4,059	$ 3,126
0.125 percent convertible senior notes principal issued related to our December 2019 debt exchange/issuance	$ —	$ —	$ 439,326
1 percent convertible senior notes principal extinguished related to our December 2019 debt exchange	$ —	$ —	$ 375,590

* We revised our 2020 and 2019 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. 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. and the consolidated results of our subsidiary, Akcea Therapeutics, Inc. and its wholly owned subsidiaries ("we", "us" or "our"). We formed Akcea in December 2014. In July 2017, Akcea completed an initial public offering, or IPO, which reduced our ownership of Akcea's common stock below 100 percent. In October 2020, we completed a merger transaction with Akcea such that following the completion of the merger, Akcea became our wholly owned subsidiary. We will refer to this transaction as the Akcea Merger throughout the remainder of this document. We reflected changes in our ownership percentage in our financial statements as an adjustment to noncontrolling interest in the period the changes occurred.

Organization and Business Activity

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

Basic and Diluted Net Income (Loss) per Share

Basic net income (loss) per share

We compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period. For the year ended December 31, 2021, we did not have to consider Akcea results separately in our calculation because we owned 100 percent of Akcea for the entire period. Our basic net loss per share for the year ended December 31, 2021 was $0.20.

For the years ended December 31, 2020 and 2019, we calculated total net income (loss) attributable to our common stockholders for each year using our net income (loss) for Ionis on a stand-alone basis plus our share of Akcea's net income (loss) for the period. To calculate the portion of Akcea's net income (loss) attributable to our ownership for each year, we multiplied Akcea's income (loss) per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net income (loss) available to Ionis common stockholders for the calculation of net income (loss) per share is different than net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders in our consolidated statements of operations for each year.

We calculated our basic net loss per share for the year ended December 31, 2020 as follows (in thousands, except per share amounts):

Year Ended December 31, 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation
Akcea's net loss in the pre-merger period attributable to our ownership	77,095	$ (1.45)	$ (111,775)
Akcea's net loss in the post-merger period attributable to our ownership			(85,987)
Akcea's total net loss attributable to our ownership			$ (197,762)
Ionis' stand-alone net loss			(246,702)
Net loss available to Ionis common stockholders			$ (444,464)
Weighted average shares outstanding			139,612
Basic net loss per share			$ (3.18)

We calculated our basic net income per share for the year ended December 31, 2019 as follows (in thousands, except per share amounts):

Year Ended December 31, 2019	Weighted Average Shares Owned in Akcea	Akcea's Net Income Per Share	Basic Net Income Per Share Calculation
Common shares	70,100	$ 0.49	$ 34,073
Akcea's net income attributable to our ownership			$ 34,073
Ionis' stand-alone net income			246,487
Net income available to Ionis common stockholders			$ 280,560
Weighted average shares outstanding			139,998
Basic net income per share			$ 2.00

Diluted net income (loss) per share

For the years ended December 31, 2021 and 2020, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock underlying the following would have had an anti-dilutive effect on net loss per share:

- 0.125 percent convertible senior notes, or 0.125% Notes;
- Note hedges related to the 0.125% Notes;
- 1 percent convertible senior notes, or 1% Notes;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs;
- Unvested performance restricted stock units, or PRSUs; and
- Employee Stock Purchase Plan, or ESPP.

For the year ended December 31, 2021, common stock underlying the following would also have had an anti-dilutive effect on net loss per share:

- 0 percent convertible senior notes, or 0% Notes; and
- Note hedges related to the 0% Notes.

Additionally as of December 31, 2021, we had warrants related to our 0 percent and 0.125 percent Notes outstanding. We will include the shares issuable under these warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

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

Year Ended December 31, 2019	Net Income Available to Ionis Common Stockholders (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 280,560	139,998	$ 2.00
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	2,090	
Shares issuable upon restricted stock award issuance	—	766	
Shares issuable related to our ESPP	—	18	
Shares issuable related to our 0.125 percent convertible notes	860	217	
Shares issuable related to our 1 percent convertible notes	9,527	10,075	
	$ 290,947	153,164	$ 1.90

Revenue Recognition

Our Revenue Sources

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

At contract inception, we analyze our collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of ASC Topic 808, Collaborative Arrangements (ASC 808). For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration reflect a vendor-customer relationship and therefore within the scope of ASC 606. When we determine elements of a collaboration do not reflect a vendor-customer relationship, we consistently apply the reasonable and rational policy election we made by analogizing to authoritative accounting literature.

We evaluate the income statement classification for presentation of amounts due from or owed to other participants associated with multiple activities in a collaboration arrangement based on the nature of each separate activity. For example, in our eplontersen collaboration with AstraZeneca, we recognize funding received from AstraZeneca for co-development activities as revenue. While, we recognize cost sharing payments to and from AstraZeneca associated with co-commercialization activities and co-medical affairs activities as SG&A expense and research and development expense, respectively.

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

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

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

We began commercializing TEGSEDI and WAYLIVRA in Europe in January 2021 and TEGSEDI in North America in April 2021 through distribution agreements with Swedish Orphan Biovitrum AB, or Sobi. Under our agreements, we are responsible for supplying finished goods inventory to Sobi and Sobi is responsible for selling each medicine to the end customer. As a result of these agreements, we earn a distribution fee on net sales from Sobi for each medicine.

Prior to the second quarter of 2021 in North America, we sold TEGSEDI through exclusive distribution agreements with third-party logistics companies, or 3PLs, that took title to TEGSEDI. The 3PLs then distributed TEGSEDI to a specialty pharmacy and a specialty distributor, which we collectively refer to as wholesalers, who then distributed TEGSEDI to health care providers and patients. In the United States, or U.S., we had a single 3PL as our sole customer and in Canada we also had a single 3PL as our sole customer. Prior to 2021 in Europe, we sold TEGSEDI and WAYLIVRA to hospitals and pharmacies, which were our customers, using 3PLs as distributors.

Under our collaboration agreement with PTC Therapeutics International Limited, or PTC, PTC is responsible for commercializing TEGSEDI and WAYLIVRA in Latin America and Caribbean countries. In the third quarter of 2021, we earned a $4 million milestone payment from PTC when WAYLIVRA was approved in Brazil, which we included in TEGSEDI and WAYLIVRA revenue in our consolidated statement of operations. Under our agreement, we started receiving royalties from PTC for TEGSEDI sales beginning in December 2021.

Research and development revenue under collaborative agreements

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

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

Steps to Recognize Revenue

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

1. Identify the contract

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

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

2. Identify the performance obligations

We next identify our performance obligations, which represent the distinct goods and services we are required to provide under the contract.

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

In some cases, we deliver a license at the start of an agreement. If we determine that our partner has full use of the license and we do not have any additional material performance obligations related to the license after delivery, then we consider the license to be a separate performance obligation. For example, in the fourth quarter of 2021, we received a $200 million upfront payment when we entered into an agreement with AstraZeneca to jointly develop and commercialize eplontersen. We recognized the upfront payment in full in the fourth quarter of 2021 because we did not have any remaining performance obligations after we delivered the license to AstraZeneca.

3. Determine the transaction price

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

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and/ or are usually based on scientific progress which is inherently uncertain. For example, in the fourth quarter of 2021, we earned a $10 million milestone payment from AstraZeneca when AstraZeneca advanced a target for a metabolic disease. We did not consider the milestone payment probable until AstraZeneca achieved the milestone event because advancing the target was contingent on AstraZeneca initiating a Phase 1 study and was not within our control. We recognized the milestone payment in full in the period the milestone event was achieved because we did not have any remaining performance obligations related to the milestone payment.

4. Allocate the transaction price

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

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

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

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

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

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

5. Recognize revenue

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

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

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

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

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

Under our distribution agreements with Sobi we concluded that our performance obligation is to provide services to Sobi over the term of the agreement, which includes supplying finished goods inventory to Sobi and because we retained the marketing authorization for TEGSEDI and WAYLIVRA we are responsible for leading the global commercial strategy for each medicine. We view this performance obligation as a series of distinct activities that are substantially the same. Therefore, we recognize as revenue the price Sobi pays us for the inventory when we deliver the finished goods inventory to Sobi. We also recognize distribution fee revenue based on Sobi's net sales of TEGSEDI and WAYLIVRA in the period in which the sales occurred. Under our agreements with Sobi, Sobi does not generally have a right of return.

Prior to our distribution agreements with Sobi, we recognized TEGSEDI and WAYLIVRA commercial revenue in the period when our customer obtained control of our products, which occurred at a point in time upon transfer of title to the customer. We classified payments to customers or other parties in the distribution channel for services that were distinct and priced at fair value as selling, general and administrative, or SG&A, expenses in our consolidated statements of operations. We classified payments to customers or other parties in the distribution channel that did not meet those criteria as a reduction of revenue, as discussed further below. We excluded from revenues taxes collected from customers relating to TEGSEDI and WAYLIVRA commercial revenue and remitted these amounts to governmental authorities.

Reserves for TEGSEDI and WAYLIVRA commercial revenue

Prior to our distribution agreements with Sobi, we recorded TEGSEDI and WAYLIVRA commercial revenue at our net sales price, or transaction price. We included in our transaction price estimated reserves for discounts, returns, chargebacks, rebates and other allowances that we offered within contracts between us and our customers, wholesalers, distributors, health care providers and other indirect customers. We estimated our reserves using the amounts we have earned or we could claim on the associated sales. We classified our reserves as a reduction of accounts receivable when we were not required to make a payment or as a current liability when we were required to make a payment. In certain cases, our estimates included a range of possible outcomes that were 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 reflected our best estimates under the terms of our respective contracts. When calculating our reserves and related TEGSEDI and WAYLIVRA commercial revenue, we only recognized amounts to the extent that we considered it probable that we would not have to reverse a significant amount of the cumulative sales we previously recognized in a future period. Under our agreements with Sobi, we transferred all reserves to Sobi.

The following were the components of variable consideration related to TEGSEDI and WAYLIVRA product sales prior to our agreements with Sobi:

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

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

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

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

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

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

Research and development revenue under collaboration agreements:

Upfront payments

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

Milestone payments

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

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, in the fourth quarter of 2021, we achieved a $7.5 million milestone payment from Biogen when we advanced a target under our 2018 strategic collaboration. We added this payment to the transaction price and allocated it to our R&D services performance obligation. We are recognizing revenue related to this milestone payment over our estimated period of performance.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation. For example, in the fourth quarter of 2021, we recognized $15 million in milestone payments when Biogen advanced two targets under our 2018 strategic collaboration. We concluded that the milestone payments were not related to our R&D services performance obligation. Therefore, we recognized the milestone payments in full in the fourth quarter of 2021.

License fees

We generally recognize as revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner. This is because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery. For example, in the fourth quarter of 2021, we earned a $60 million license fee from Biogen when Biogen licensed ION306, an investigational medicine in development to treat SMA.

Sublicense fees

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

Amendments to Agreements

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

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

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

For example, in May 2015, we entered into an exclusive license agreement with Bayer to develop and commercialize IONIS-FXI$_{Rx}$ for the prevention of thrombosis. As part of the agreement, Bayer paid us a $100 million upfront payment. At the onset of the agreement, we were responsible for completing a Phase 2 study of IONIS-FXI$_{Rx}$ in people with end-stage renal disease on hemodialysis and for providing an initial supply of API. In February 2017, we amended our agreement with Bayer to advance IONIS-FXI$_{Rx}$ and to initiate development of fesomersen, 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 fesomersen. Under the 2017 amendment, we concluded we had a new agreement with three performance obligations. These performance obligations were to deliver the license of fesomersen, 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 the Bayer collaboration.

Multiple agreements

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

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

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

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

Contracts Receivable

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

As of December 31, 2021, approximately 93.8 percent of our contracts receivables were from two significant customers. As of December 31, 2020, approximately 99.5 percent of our contracts receivables were from two significant customers.

Unbilled SPINRAZA Royalties

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

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue on our consolidated balance sheet. During the years ended December 31, 2021 and 2020, we recognized $98.1 million and $100.4 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. For further discussion, refer to our revenue recognition policy above.

Cost of Sales

Our cost of sales includes manufacturing costs, transportation and freight costs and indirect overhead costs associated with the manufacturing and distribution of our products. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of sales. We also may include certain period costs related to manufacturing services and inventory adjustments in cost of sales.

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, 2021, 2020 and 2019, research and development expenses were $638.2 million, $531.0 million and $461.5 million, respectively. A portion of the costs included in research and development expenses are costs associated with 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 10.2 years at December 31, 2021.

The cost of our patents capitalized on our consolidated balance sheet at December 31, 2021 and 2020 was $38.4 million and $37.0 million, respectively. Accumulated amortization related to patents was $9.4 million and $9.1 million at December 31, 2021 and 2020, respectively.

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

Year Ending December 31,	Amortization (in millions)
2022	$ 2.2
2023	$ 2.1
2024	$ 1.9
2025	$ 1.8
2026	$ 1.8

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 2021, 2020 and 2019, patent expenses were $5.3 million, $4.1 million and $4.2 million, respectively, and included non-cash charges related to the write-down of our patent costs to their estimated net realizable values of $2.7 million, $1.9 million and $2.2 million, respectively.

Accrued Liabilities

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

	December 31,	
	2021	2020
Clinical expenses	$ 65,730	$ 39,477
In-licensing expenses	8,044	8,264
Commercial expenses	2,471	11,559
Other miscellaneous expenses	12,315	30,861
Total accrued liabilities	$ 88,560	$ 90,161

Estimated Liability for Clinical Development Costs

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

Noncontrolling Interest in Akcea Therapeutics, Inc.

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

Concentration of Credit Risk

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

Cash, Cash Equivalents and Investments

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

We also have equity investments of less than 20 percent ownership in publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At December 31, 2021, we held equity investments in three publicly held companies, Antisense Therapeutics Limited, or ATL, Bicycle Therapeutics plc, or Bicycle, and ProQR Therapeutics N.V., or ProQR. We also held equity investments in seven privately-held companies, Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, YourBio Health, Inc. (formerly Seventh Sense Biosystems) and Suzhou-Ribo Life Science Co, Ltd.

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

Inventory Valuation

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

We review our inventory periodically and reduce the carrying value of items we consider to be slow moving or obsolete to their estimated net realizable value based on forecasted demand compared to quantities on hand. We consider several factors in estimating the net realizable value, including shelf life of our inventory, alternative uses for our medicines in development and historical write-offs. We recorded an insignificant amount of inventory write-offs during the years ended December 31, 2021 and 2020.

Our inventory consisted of the following (in thousands):

	December 31,	
	2021	2020
Raw materials:		
Raw materials- clinical	$ 14,507	$ 9,206
Raw materials- commercial	4,139	7,502
Total raw materials	18,646	16,708
Work in process	5,770	2,252
Finished goods	390	3,005
Total inventory	$ 24,806	$ 21,965

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, 2021	December 31, 2020
Computer software, laboratory, manufacturing and other equipment	3 to 10	$ 72,802	$ 68,990
Building, building improvements and building systems	15 to 40	144,046	137,879
Land improvements	20	10,077	8,391
Leasehold improvements	5 to 15	20,144	17,263
Furniture and fixtures	5 to 10	10,591	12,871
		257,660	245,394
Less accumulated depreciation		(102,653)	(87,379)
		155,007	158,015
Land		23,062	23,062
Total		$ 178,069	$ 181,077

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

Fair Value of Financial Instruments

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

Leases

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

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

Long-Lived Assets

We evaluate long-lived assets, which include property, plant and equipment and patent costs, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets. We recorded charges of $2.7 million, $1.9 million and $2.2 million for the years ended December 31, 2021, 2020 and 2019, respectively, related to the write-down of patents.

Use of Estimates

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the U.S. that require us to make estimates and assumptions that affect the amounts reported in our consolidated financial statements and accompanying notes. Actual results could differ from our estimates.

Stock-Based Compensation Expense

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

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

We recognize compensation expense for stock options granted, RSUs, PRSUs 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.

In December 2020, we amended and restated the Akcea 2015 equity plan, including renaming the plan as the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, or 2020 Plan. As a result, all employees are now under an Ionis stock plan and subject to the same Black-Scholes assumptions.

RSU's:

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 to employees vest annually over a four-year period. The RSUs we granted to our board of directors prior to June 2020 vest annually over a four-year period. RSUs granted to our board of directors after June 2020 fully vest after one year.

PRSU's:

Beginning in 2020, we added PRSU awards to the compensation for our Chief Executive Officer, Dr. Brett Monia. Under the terms of the grants, one third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (i.e., the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on our relative total shareholder return, or TSR, as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. Under the terms of the grants no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150 percent of the target number depending on our relative TSR.

We determined the fair value of Dr. Monia's PRSUs using a Monte Carlo model because the performance target is based on our relative TSR, which represents a market condition. We are recognizing the grant date fair value of these awards as stock-based compensation expense using the accelerated multiple-option approach over the vesting period. The weighted-average grant date fair value of PRSUs granted to Dr. Monia for the years ended December 31, 2021 and 2020 were $77.17 and $93.09 per share, respectively.

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

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss is comprised of unrealized gains and losses on investments, net of taxes and currency translation adjustments. The following table summarizes changes in accumulated other comprehensive loss for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Beginning balance accumulated other comprehensive loss	$ (21,071)	$ (25,290)	$ (32,016)
Unrealized gains (losses) on securities, net of tax (1)	(11,486)	3,729	6,633
Currency translation adjustment	(111)	617	93
Adjustments to other comprehensive loss from purchase of noncontrolling interest of Akcea Therapeutics, Inc.	—	(127)	—
Net other comprehensive loss for the period	(11,597)	4,219	6,726
Ending balance accumulated other comprehensive loss	$ (32,668)	$ (21,071)	$ (25,290)

(1) We did not have tax expense included in our other comprehensive loss for the years ended December 31, 2021 and 2020. For the year ended December 31, 2019, we had a tax benefit of $1.4 million included in other comprehensive loss.

Convertible Debt

Adoption of ASU 2020-06

In August 2020, the FASB issued ASU 2020-06, which simplifies the accounting for convertible debt instruments, amends the guidance on derivative scope exceptions for contracts in an entity's own equity, and modifies the guidance on diluted earnings per share calculations. We adopted ASU 2020-06 on January 1, 2021 under the full retrospective approach, which required us to revise our prior period financial statements. This guidance impacted our accounting for outstanding convertible debt. At January 1, 2021, we had two outstanding convertible notes, our 0.125% Notes, which mature in December 2024, and our 1% Notes, which matured in November 2021. In April 2021, we completed a $632.5 million offering of 0% Notes primarily to repurchase a majority of our 1% Notes. We accounted for our 0% Notes under ASU 2020-06 at issuance. Refer to Note 3, *Long-Term Obligations and Commitments*, for further information.

The updated guidance eliminates the cash conversion accounting model we previously followed in Accounting Standard Codification, or ASC, 470-20, which required us to separate each of our convertible debt instruments at issuance into two units of accounting, a liability component, based on our nonconvertible debt borrowing rate at issuance, and an equity component. Under ASU 2020-06, we now account for each of our convertible debt instruments as a single unit of accounting, a liability, because we concluded that the conversion features do not require bifurcation as a derivative under ASC 815-15 and we did not issue our convertible debt instruments at a substantial premium. Since we adopted ASU 2020-06 using the full retrospective approach, we were required to apply the guidance to all convertible debt instruments we had outstanding as of January 1, 2019. We recomputed the basis of each convertible debt instrument as if we accounted for each as a single unit of accounting at issuance. This update included recalculating the amortization of debt issuance costs using an updated effective interest rate. As a result of adopting ASU 2020-06, we recorded a cumulative adjustment to decrease our additional paid in capital and our accumulated deficit at January 1, 2019. We have updated these financial statements to reflect the cumulative adjustment for the periods presented. We have labeled our prior period financial statements "as revised" to indicate the change required under the new accounting guidance. Below is a summary of the change in our balance sheet at December 31, 2020 and statement of operations from the years ended December 31, 2020 and 2019 under the ASC 470-20 legacy guidance compared to the new ASU 2020-06 guidance we adopted:

The following table summarizes the adjustments we made to the consolidated balance sheet we originally reported at December 31, 2020 to adopt ASU 2020-06 (in thousands):

	December 31, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
1 percent convertible senior notes	$ 293,161	$ 15,648	$ 308,809
0.125 percent convertible senior notes	$ 455,719	$ 84,417	$ 540,136
Additional paid-in-capital	$ 2,113,646	$ (218,127)	$ 1,895,519
Accumulated deficit	$ (1,249,368)	$ 118,062	$ (1,131,306)

Under ASU 2020-06, our revised ending balances for our 1% Notes and 0.125% Notes as of December 31, 2020 represent the principal balance of each convertible debt instrument less debt issuance costs. Additionally, because we have deferred tax assets related to our convertible debt instruments, we also adjusted these amounts as part of our adoption of ASU 2020-06. However, because we have a full valuation allowance on our deferred tax assets, there was no impact to our consolidated balance sheet related to our deferred tax assets.

The following tables summarize the adjustments we made to the consolidated statement of operations we originally reported for the years ended December 31, 2020 and 2019 to adopt ASU 2020-06 (in thousands):

	Year Ended December 31, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Interest expense	$ (44,990)	$ 35,480	$ (9,510)
Loss before income tax expense	$ (170,032)	$ 35,480	$ (134,552)
Income tax expense	$ (316,734)	$ (28,457)	$ (345,191)
Net loss	$ (486,766)	$ 7,023	$ (479,743)
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ (451,286)	$ 7,023	$ (444,263)
Basic and diluted net loss per share	$ (3.23)	$ 0.05	$ (3.18)

	Year Ended December 31, 2019		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Interest expense	$ (48,768)	$ 36,328	$ (12,440)
Loss on early retirement of debt	(21,865)	(44,331)	(66,196)
Income before income tax benefit (expense)	$ 346,769	$ (8,003)	$ 338,766
Income tax expense	$ (43,507)	$ (8,000)	$ (51,507)
Net income	$ 303,262	$ (16,003)	$ 287,259
Net income attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 294,146	$ (16,003)	$ 278,143
Basic net income per share	2.12	(0.12)	2.00
Diluted net income per share	$ 2.08	$ (0.18)	$ 1.90

Under ASU 2020-06, our revised interest expense is lower because we are no longer recording non-cash interest expense related to a debt discount. This decrease was partially offset by the increase in interest expense related to the amortization of debt issuance costs because we no longer allocate a portion of our debt issuance costs to stockholders' equity at issuance. Instead, the entire debt issuance costs were recorded as a contra-liability on our consolidated balance sheet at issuance and we are amortizing them over the contractual term using an updated effective interest rate. Our updated effective interest rates for our 1% Notes and 0.125% Notes were 1.4 percent and 0.5 percent, respectively.

The following tables summarize the adjustments we made to our consolidated statements of stockholders' equity we originally reported at December 31, 2020 and 2019 to adopt ASU 2020-06 (in thousands):

	December 31, 2020		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Additional paid-in-capital	$ 2,113,646	$ (218,127)	$ 1,895,519
Accumulated deficit	$ (1,249,368)	$ 118,062	$ (1,131,306)
Total stockholders' equity	$ 843,347	$ (100,065)	$ 743,282

	December 31, 2019		
	As Previously Reported	ASU 2020-06 Adjustment	As Revised
Additional paid-in-capital	$ 2,203,778	$ (218,128)	$ 1,985,650
Accumulated deficit	$ (707,534)	$ 111,039	$ (596,495)
Total stockholders' equity	$ 1,684,547	$ (107,088)	$ 1,577,459

Call Spread

In conjunction with the issuance of our 0% Notes and 0.125% Notes in April 2021 and December 2019, respectively, we entered into call spread transactions, which were comprised of purchasing note hedges and selling warrants. We account for the note hedges and warrants as separate freestanding financial instruments and treat each instrument as a separate unit of accounting. We determined that the note hedges and warrants do not meet the definition of a liability using the guidance contained in ASC Topic 480; therefore, we account for the note hedges and warrants using the Derivatives and Hedging – Contracts in Entity's Own Equity accounting guidance contained in ASC Topic 815. We determined that the note hedges and warrants meet the definition of a derivative, are indexed to our stock and meet the criteria to be classified in shareholders' equity. We recorded the aggregate amount paid for the note hedges and the aggregate amount received for the warrants as additional paid-in capital in our consolidated balance sheet. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Segment Information

In 2021, we began operating as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment. Previously, we had operated as two operating segments, Ionis Core and Akcea Therapeutics. We completed the Akcea Merger in October 2020 and fully integrated Akcea's operations into ours as of January 1, 2021.

Fair Value Measurements

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

The following tables present the major security types we held at December 31, 2021 and 2020 that we regularly measure and carry at fair value. As of December 31, 2021, our Bicycle investment was subject to trading restrictions that extend to the third quarter of 2022; as a result, we included a lack of marketability discount in valuing this investment, which is a Level 3 input. As of December 31, 2020, we did not have any investments that we valued using Level 3 inputs. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At December 31, 2021	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents (1)	$ 541,199	$ 541,199	$ —	$ —
Corporate debt securities (2)	764,059	—	764,059	—
Debt securities issued by U.S. government agencies (2)	120,868	—	120,868	—
Debt securities issued by the U.S. Treasury (2)	182,634	182,634	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	174,464	—	174,464	—
Other municipal debt securities (2)	6,099	—	6,099	—
Investment in Bicycle Therapeutics plc (4)	14,330	—	—	14,330
Investment in ProQR Therapeutics N.V. (4)	3,875	3,875	—	—
Total	$ 1,807,528	$ 727,708	$ 1,065,490	$ 14,330

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

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

(2) Included in short-term investments.

(3) $2.3 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

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

(5) $10.0 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

(6) $17.5 million included in cash and cash equivalents on our consolidated balance sheet, with the difference included in short-term investments on our consolidated balance sheet.

Convertible Notes

Our 0.125% Notes and 0% Notes had a fair value of $495.4 million and $559.2 million at December 31, 2021, respectively. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

Income Taxes

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

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

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

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

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

Impact of Recently Issued Accounting Standards

As disclosed in the “Convertible Debt” policy above within this footnote, we adopted the simplified accounting for convertible debt instrument guidance (ASU 2020-06) on January 1, 2021. Refer to the section above for the impact of adoption. We do not expect any other recently issued accounting standards to have a material impact to our financial results.

2. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2021:

One year or less	51%
After one year but within two years	34%
After two years but within three and a half years	15%
Total	100%

As illustrated above, at December 31, 2021, 85 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, 2021, we had an ownership interest of less than 20 percent in seven private companies and three public companies with which we conduct business. The privately-held companies are Aro Biotherapeutics, Atlantic Pharmaceuticals Limited, Dynacure SAS, Empirico, Inc., Flamingo Therapeutics BV, YourBio Health, Inc. and Suzhou-Ribo Life Science Co, Ltd. The publicly traded companies are Antisense Therapeutics Ltd., Bicycle and ProQR.

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

December 31, 2021	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (1)	$ 383,870	$ 728	$ (226)	$ 384,372
Debt securities issued by U.S. government agencies	48,493	19	(18)	48,494
Debt securities issued by the U.S. Treasury (1)	45,424	—	(64)	45,360
Debt securities issued by states of the U.S. and political subdivisions of the states	134,770	45	(37)	134,778
Total securities with a maturity of one year or less	612,557	792	(345)	613,004
Corporate debt securities	382,000	331	(2,644)	379,687
Debt securities issued by U.S. government agencies	72,935	—	(561)	72,374
Debt securities issued by the U.S. Treasury	137,635	139	(500)	137,274
Debt securities issued by states of the U.S. and political subdivisions of the states	39,909	1	(224)	39,686
Other municipal debt securities	6,136	—	(37)	6,099
Total securities with a maturity of more than one year	638,615	471	(3,966)	635,120
Total available-for-sale securities	$ 1,251,172	$ 1,263	$ (4,311)	$ 1,248,124
Equity securities:				
Total equity securities included in other current assets (2)	$ 11,897	$ 7,145	$ (837)	$ 18,205
Total equity securities included in deposits and other assets (3)	15,615	16,707	—	32,322
Total equity securities	$ 27,512	$ 23,852	$ (837)	$ 50,527
Total available-for-sale and equity securities	$ 1,278,684	$ 25,115	$ (5,148)	$ 1,298,651

December 31, 2020	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (1)	$ 514,182	$ 2,194	$ (41)	$ 516,335
Debt securities issued by U.S. government agencies	94,234	354	(2)	94,586
Debt securities issued by the U.S. Treasury (1)	307,576	233	(9)	307,800
Debt securities issued by states of the U.S. and political subdivisions of the states	104,271	196	(12)	104,455
Other municipal debt securities	5,191	—	(7)	5,184
Total securities with a maturity of one year or less	1,025,454	2,977	(71)	1,028,360
Corporate debt securities	325,079	4,941	(40)	329,980
Debt securities issued by U.S. government agencies	80,099	185	(9)	80,275
Debt securities issued by the U.S. Treasury	50,318	383	(4)	50,697
Debt securities issued by states of the U.S. and political subdivisions of the states	31,779	91	(16)	31,854
Other municipal debt securities	1,041	—	—	1,041
Total securities with a maturity of more than one year	488,316	5,600	(69)	493,847
Total available-for-sale securities	$ 1,513,770	$ 8,577	$ (140)	$ 1,522,207
Equity securities:				
Total equity securities included in other current assets (2)	$ 4,712	$ —	$ (2,681)	$ 2,031
Total equity securities included in deposits and other assets (3)	15,062	15,938	—	31,000
Total equity securities	$ 19,774	$ 15,938	$ (2,681)	$ 33,031
Total available-for-sale and equity securities	$ 1,533,544	$ 24,515	$ (2,821)	$ 1,555,238

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

(2) Our equity securities included in other current assets consisted of our investments in publicly traded companies. We recognize publicly traded equity securities at fair value.

(3) Our equity securities included in deposits and other assets consisted of our investments in privately held companies. We recognize our private company equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer on our consolidated balance sheet.

The following is a summary of our investments we considered to be temporarily impaired at December 31, 2021 (in thousands). All of these investments have less than 12 months of temporary impairment. We believe that the decline in value of these securities is temporary and is primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

	Number of Investments	Estimated Fair Value	Unrealized Losses
Corporate debt securities	272	$ 552,966	$ (2,870)
Debt securities issued by U.S. government agencies	15	114,338	(579)
Debt securities issued by the U.S. Treasury	13	134,987	(564)
Debt securities issued by states of the U.S. and political subdivisions of the states	425	126,401	(261)
Other municipal debt securities	2	6,099	(37)
Total temporarily impaired securities	727	$ 934,791	$ (4,311)

3. Long-Term Obligations and Commitments

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

	December 31,	
	2021	2020 (as revised*)
0.125 percent convertible senior notes	$ 542,314	$ 540,136
1 percent convertible senior notes (1)	—	308,809
0 percent convertible senior notes	619,119	—
Long-term mortgage debt	59,713	59,984
Leases and other obligations	29,904	30,710
Total	$ 1,251,050	$ 939,639
Less: current portion (1)	(3,526)	(316,110)
Total Long-Term Obligations	$ 1,247,524	$ 623,529

(1) We classified the carrying value of our 1% Notes as a current liability on our consolidated balance sheet at December 31, 2020 because it matured in November 2021.

* We revised our 2020 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

Convertible Debt and Call Spread

0 Percent Convertible Senior Notes and Call Spread

In April 2021, we completed a $632.5 million offering of convertible senior notes. We used a portion of the net proceeds from the issuance of the 0% Notes to repurchase $247.9 million in principal of our 1% Notes for $257.0 million.

At December 31, 2021, we had the following 0% Notes outstanding (amounts in millions except interest rate and price per share data):

	0% Notes
Outstanding principal balance	$ 632.5
Unamortized debt issuance costs	$ 13.4
Maturity date	April 2026
Interest rate	0 percent
Effective interest rate	0.5 percent
Conversion price per share	$ 57.84
Effective conversion price per share with call spread	$ 76.39
Total shares of common stock subject to conversion	10.9

In conjunction with the April 2021 offering, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0% Notes by increasing the effective conversion price on our 0% Notes. We increased our effective conversion price to $76.39 with the same number of underlying shares as our 0% Notes. The call spread cost us $46.9 million, of which $136.7 million was for the note hedge purchase, offset by $89.8 million we received for selling the warrants. Similar to our 0% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0% Notes. The note hedges will expire upon maturity of the 0% Notes, or April 2026. The note hedges and warrants are separate transactions and are not part of the terms of our 0% Notes. The holders of the 0% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our consolidated balance sheet. See our Call Spread accounting policy in Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

0.125 Percent Convertible Senior Notes and Call Spread

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes.

At December 31, 2021, we had the following 0.125% Notes outstanding with interest payable semi-annually (amounts in millions except interest rate and price per share data):

	0.125% Notes
Outstanding principal balance	$ 548.8
Unamortized debt issuance costs	$ 6.5
Maturity date	December 2024
Interest rate	0.125 percent
Effective interest rate	0.5 percent
Conversion price per share	$ 83.28
Effective conversion price per share with call spread	$ 123.38
Total shares of common stock subject to conversion	6.6

In conjunction with the issuance of our 0.125% Notes in December 2019, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the effective conversion price on our 0.125% Notes. We increased our effective conversion price to $123.38 with the same number of underlying shares as our 0.125% Notes. The call spread cost us $52.6 million, of which $108.7 million was for the note hedge purchase, offset by $56.1 million we received for selling the warrants. Similar to our 0.125% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0.125% Notes. The note hedges will expire upon maturity of the 0.125% Notes, or December 2024. The note hedges and warrants are separate transactions and are not part of the terms of our 0.125% Notes. The holders of the 0.125% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our consolidated balance sheet. See our Call Spread accounting policy in Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

1 Percent Convertible Senior Notes

In November 2014, we completed a $500 million offering of convertible senior notes, which matured in 2021 and beared interest at 1 percent with interest payable semi-annually. In December 2016, we issued an additional $185.5 million of 1% Notes in exchange for the redemption of a portion of our previously outstanding 2.75% convertible senior notes, or 2.75% Notes. In December 2019, we exchanged a portion of our 1% Notes for new 0.125% Notes. As a result, the principal balance of 1% Notes was $309.9 million. Additionally, we recorded a $66.2 million non-cash loss on the early retirement of debt, reflecting the early retirement of a significant portion of our 1% Notes in December 2019. The non-cash loss on the early retirement of our debt is the difference between the amount paid to exchange our 1% Notes and the net carrying balance of the liability at the time that we completed the debt exchange.

In April 2021, we repurchased $247.9 million in aggregate principal amount of our 1% Notes in privately negotiated transactions. As a result of the repurchase, we recognized an $8.6 million loss on early retirement of debt, reflecting the early retirement of a significant portion of our 1% Notes. The loss on the early retirement of our debt is the difference between the amount paid to retire our 1% Notes and the net carrying balance of the liability at the time that we retired the debt. We paid the remaining principal balance of our 1% Notes with $62.0 million of cash at maturity in November 2021.

Other Terms of Convertible Senior Notes

The 0% and 0.125% Notes are convertible under certain conditions, at the option of the note holders. We can 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 notes prior to maturity, and we do not have to provide a sinking fund for them. Holders of the notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indentures governing the notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus any accrued and unpaid interest. The 1% Notes were subject to similar terms.

Our total interest expense for our outstanding senior convertible notes for the years ended December 31, 2021, 2020 and 2019 included $4.9 million, $3.2 million and $2.9 million, respectively, of non-cash interest expense related to the amortization of debt issuance costs for our convertible notes.

Financing Arrangements

Research and Development and Manufacturing Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million and our manufacturing facility for $14.0 million. We financed the purchase of these two facilities with mortgage debt of $60.4 million in total. Our primary R&D facility mortgage has an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages, we are only required to make interest payments. We will begin making principal payments in 2022. Both mortgages mature in August 2027.

Maturity Schedules

Annual debt and other obligation maturities, including fixed and determinable interest, at December 31, 2021 are as follows (in thousands):

2022	$ 3,498
2023	4,180
2024	4,180
2025	1,184,820
2026	3,494
Thereafter	57,439
Subtotal	$ 1,257,611
Less: current portion	(3,526)
Less: fixed and determinable interest	(15,498)
Less: debt issuance costs	(20,302)
Plus: lease liabilities	22,058
Plus: other liabilities	7,181
Total long-term debt	$ 1,247,524

Operating Leases

Carlsbad Leases

We lease a facility adjacent to our manufacturing facility that has laboratory and office space that we use to support our manufacturing facility. We lease this space under a non-cancelable operating lease. In May 2020, we exercised our option to extend our lease, extending our lease term from June 2021 to August 2026. We have one remaining option to extend the lease for an additional five-year period.

We also lease additional office spaces in Carlsbad. We lease these spaces under non-cancelable operating leases with initial terms ending in 2023 with options to extend each of the leases for one five-year period.

Boston Leases

We entered into an operating lease agreement for office space located in Boston, Massachusetts in the second quarter of 2018. The lease commencement date was in August 2018 and we took occupancy in September 2018. We are leasing this space under a non-cancelable operating lease with an initial term ending after 123 months and an option to extend the lease for an additional five-year term. Under the lease agreement, we received a three-month free rent period, which commenced on August 15, 2018, and a tenant improvement allowance up to $3.8 million.

In January 2022, we entered into a sublease agreement for our office space located in Boston, Massachusetts. The sublease commencement date was in January 2022 when the office space was ready for our tenant's occupancy. We are subleasing this space under a non-cancelable operating sublease with a sublease term ending 83 months following the sublease commencement date with no option to extend the sublease. Under the sublease agreement we provided a seven-month free rent period, which commenced on January 6, 2022. We will receive lease payments over the sublease term totaling $9.6 million.

In September 2021, we entered into an operating lease agreement for another office space located in Boston, Massachusetts. The lease commencement date was in November 2021 when the office space was ready for our occupancy. We are leasing this space under a non-cancelable operating lease with an initial term ending 91 months following the lease commencement date and an option to extend the lease for an additional five-year term. Under the lease agreement, we will receive a seven-month free rent period, which commenced on November 1, 2021. Our lease payments over the initial term total $6.8 million. We recognized a right-of-use lease asset and lease liability in the fourth quarter of 2021 upon the lease commencement date.

When we determined our lease term for our operating lease right-of-use assets and lease liabilities for these leases, we did not include the extension options for these leases in the original lease term.

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

		At December 31, 2021
Right-of-use operating lease assets (1)	$	18.0
Operating lease liabilities (2)	$	22.1
Weighted average remaining lease term		6.6 years
Weighted average discount rate		6.0%

(1) Included in deposits and other assets on our consolidated balance sheet.

(2) Current portion of $2.6 million was included in current portion of long-term obligations on our consolidated balance sheet, with the difference included in long-term obligations.

During the years ended December 31, 2021, 2020, and 2019 we paid $3.3 million, $3.8 million and $3.9 million of lease payments, which were included in operating activities in our consolidated statements of cash flows.

As of December 31, 2021, the future payments for our operating lease liabilities are as follows (in thousands):

	Operating Leases
Year ending December 31,	$
2022	4,075
2023	4,314
2024	4,223
2025	4,062
2026	3,778
Thereafter	7,035
Total minimum lease payments	27,487
Less:	
Imputed interest	(5,429)
Total operating lease liabilities	$ 22,058

Rent expense was $3.4 million, $3.7 million and $3.6 million for the years ended December 31, 2021, 2020 and 2019, respectively.

4. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15 million shares of "blank check" Preferred Stock. As of December 31, 2021, 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, 2021.

Common Stock

At December 31, 2021 and 2020, we had 300 million shares of common stock authorized, of which 141.2 million and 140.4 million were issued and outstanding, respectively. As of December 31, 2021, total common shares reserved for future issuance were 46.2 million.

During the years ended December 31, 2021, 2020 and 2019, we issued 1.1 million, 1.7 million and 3.1 million shares of common stock, respectively, for stock option exercises, vesting of restricted stock units, and ESPP purchases. We received net proceeds from these transactions of $11.6 million, $52.0 million and $119.7 million in 2021, 2020 and 2019, respectively.

Share Repurchase Program

In September 2019, our board of directors approved a share repurchase program of up to $125 million of our common stock. In 2019, we repurchased 535,000 shares for $34.4 million. In the first quarter of 2020, we repurchased an additional 1.5 million shares for $90.5 million.

Stock Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20.0 million shares of common stock to our employees, directors, and consultants. The plan expires in January 2024. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. At December 31, 2021, a total of 28 thousand options were outstanding, of which options to purchase 28 thousand shares were exercisable, and 49 thousand shares were available for future grant under the 1989 Plan.

2011 Equity Incentive Plan

In March 2011, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, and performance cash awards to our employees, directors, and consultants. In June 2015, May 2017 and June 2019, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan, or 2011 Plan, to increase the total number of shares reserved for issuance. We increased the shares available under our 2011 Equity Incentive Plan from 5.5 million to 11.0 million in June 2015, from 11.0 million to 16.0 million in May 2017 and from 16.0 million to 23.0 million in June 2019. In the second quarter of 2021, after receiving approval from our stockholders, we amended our 2011 Plan. The amendment increased the total number of shares of common stock authorized for issuance under the 2011 Plan from 23.0 million to 29.7 million and added a fungible share counting ratio whereby the share reserve will be reduced by 1.7 shares for each share of common stock issued pursuant to a full value award (i.e., RSU or PRSU) and increased by 1.7 shares for each share of common stock returning from a full value award. The plan expires in June 2031. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only stock options, RSU and PRSU awards to our employees, directors and consultants. 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. Options granted after December 31, 2021 have a term of ten 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, 2021, a total of 12.8 million options were outstanding, of which 8.3 million were exercisable, 2.5 million restricted stock unit awards were outstanding, and 8.5 million shares were available for future grant under the 2011 Plan.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. The stock options and restricted stock unit awards we issued to Dr. Stanley T. Crooke in his former role as chief executive officer and certain stock options and restricted stock unit awards we issued to B. Lynne Parshall in her former role as chief operating officer have accelerated vesting upon a change of control, as defined in the 2011 Plan. In addition, we implemented a change of control and severance benefit plan that provides for change of control and severance benefits to our executive officers, including our chief executive officer and chief financial officer. If we terminate one of our executive officers or if an executive officer resigns for good reason during the period that begins three months before and ends twelve months following a change in control of the company, the impacted executive officers' stock options and RSUs vesting will accelerate for options and RSUs outstanding as of the termination date.

2020 Equity Incentive Plan

In connection with the Akcea Merger in October 2020, we assumed the unallocated portion of the available share reserve under the Akcea 2015 Equity Incentive Plan. In December 2020, we amended and restated the Akcea 2015 equity plan, including renaming the plan as the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, or 2020 Plan. The 2020 Plan provided for the issuance of up to 2.6 million shares of our Common Stock to our employees, directors and consultants who were employees of Akcea prior to the Akcea Merger. In the second quarter of 2021, our Compensation Committee approved an amendment to the 2020 Plan. The amendment decreased the total number of shares of common stock authorized for issuance under the 2020 Plan from approximately 2.6 million to 1.6 million. We assumed the 2020 Plan in connection with Ionis' reacquisition of all of the outstanding shares of Akcea Therapeutics, Inc. as part of the Akcea Merger.

The plan expires in December 2025. The 2020 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only stock options and RSU awards to our eligible employees, directors and consultants. 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. Options granted after December 31, 2021 have a term of ten years. We have granted restricted stock unit awards to our employees under the 2020 Plan which vest annually over a four-year period. At December 31, 2021, a total of 0.2 million options were outstanding, of which none were exercisable, 0.1 million restricted stock unit awards were outstanding, and 1.3 million shares were available for future grant under the 2020 Plan.

Under the 2020 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur.

Corporate Transactions and Change in Control under 2011 and 2020 Plans

In the event of certain significant corporate transactions, our Board of Directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 and 2020 Plans:

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

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan, or the 2002 Plan. In June 2015, after receiving approval from our stockholders, we amended our 2002 Plan to increase the total number of shares reserved for issuance from 1.2 million to 2.0 million. In June 2020, after receiving approval from our stockholders, we further amended our 2002 Plan. The amendments included:

- An increase to the total number of shares reserved for issuance under the plan from 2.0 million to 2.8 million shares;
- A reduction to the amount of the automatic awards under the plan;
- A revision to the vesting schedule of new awards granted; and
- An extension of the term of the plan.

Options under this plan expire 10 years from the date of grant. At December 31, 2021, a total of 1.0 million options were outstanding, of which 0.8 million were exercisable, 0.1 million restricted stock unit awards were outstanding, and 0.7 million shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years until 2019, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 3.2 million shares authorized under the plan as of December 31, 2021. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10percent of each employee's compensation) at the lower of 85percent of fair market value at the beginning of the purchase period or the end of each purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase. During 2021, employees purchased and we issued to employees 0.07 million shares under the ESPP at a weighted average price of $39.26 per share. At December 31, 2021, there were 0.6 million shares available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity under our stock plans for the year ended December 31, 2021 (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, 2020	12,439	$ 54.11		
Granted	3,382	$ 53.07		
Exercised	(219)	$ 38.69		
Cancelled/forfeited/expired	(1,513)	$ 54.65		
Outstanding at December 31, 2021	14,089	$ 54.04	3.89	$ 1,131
Exercisable at December 31, 2021	9,175	$ 53.65	2.94	$ 1,067

The weighted-average estimated fair values of options granted were $24.35, $29.43 and $28.76 for the years ended December 31, 2021, 2020 and 2019, respectively. The total intrinsic value of options exercised during the years ended December 31, 2021, 2020 and 2019 were $2.5 million, $15.5 million and $83.8 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $8.5 million, $43.7 million and $105.9 million for the years ended December 31, 2021, 2020 and 2019, respectively. For the year ended December 31, 2021, the weighted-average fair value of options exercised was $50.13. As of December 31, 2021, total unrecognized compensation cost related to non-vested stock options was $49.6 million. We expect to recognize this cost over a weighted average period of 1.1 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2021 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2020	2,374	$ 58.81
Granted	1,548	$ 57.69
Vested	(834)	$ 57.47
Cancelled/forfeited	(411)	$ 59.24
Non-vested at December 31, 2021	2,677	$ 58.51

For the years ended December 31, 2021, 2020 and 2019, the weighted-average grant date fair value of RSUs granted was $57.69, $60.86 and $60.23 per RSU, respectively. As of December 31, 2021, total unrecognized compensation cost related to RSUs was $57.0 million. We expect to recognize this cost over a weighted average period of 1.2 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2021, 2020 and 2019 (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Cost of sales	$ 456	$ 1,991	$ 438
Research, development and patent	87,522	115,584	95,348
Selling, general and administrative	32,700	112,542	50,788
Total	$ 120,678	$ 230,117	$ 146,574

In October 2020, as part of the Akcea Merger, Akcea's outstanding equity awards vested under Akcea's Plan. As a result, in the fourth quarter of 2020, we recognized all unrecognized stock-based compensation ($59.3 million) under Akcea's Plan. See Note 7, *Akcea Merger*, in the Notes to the Consolidated Financial Statements for further details.

In the third quarter of 2019, three Akcea executive officers terminated their employment and entered into separation agreements with Akcea. As a result, in the third quarter of 2019, Akcea reversed $19.1 million of stock-based compensation expense it had previously recognized related to the executive officers' stock options and RSUs that were no longer going to vest.

Determining Fair Value

Valuation. We measure stock-based compensation expense for equity-classified awards, principally related to stock options, RSUs, PRSUs 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. See Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements for further details on how we determine the fair value of PRSUs.

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 stock options granted based on actual and projected exercise patterns. We recognize compensation expense for stock options granted, RSUs, PRSUs 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, 2021, 2020 and 2019, we used the following weighted-average assumptions in our Black-Scholes calculations:

Ionis Employee Stock Options:

	Year Ended December 31,		
	2021	2020	2019
Risk-free interest rate	0.6%	1.5%	2.3%
Dividend yield	0.0%	0.0%	0.0%
Volatility	54.0%	58.6%	60.3%
Expected life	4.9 years	4.7 years	4.8 years

Ionis Board of Director Stock Options:

	Year Ended December 31,		
	2021	2020	2019
Risk-free interest rate	1.2%	0.5%	1.9%
Dividend yield	0.0%	0.0%	0.0%
Volatility	55.9%	57.6%	60.7%
Expected life	7.3 years	6.7 years	6.6 years

Ionis ESPP:

	Year Ended December 31,		
	2021	2020	2019
Risk-free interest rate	0.1%	0.8%	2.4%
Dividend yield	0.0%	0.0%	0.0%
Volatility	42.4%	47.9%	45.6%
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.

5. Income Taxes

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

	Year Ended December 31,		
	2021	2020 (as revised*)	2019 (as revised*)
United States	$ (29,966)	$ (137,222)	$ 336,277
Foreign	818	2,670	2,489
Income (loss) before income taxes	$ (29,148)	$ (134,552)	$ 338,766

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

	Year Ended December 31,		
	2021	2020 (as revised*)	2019 (as revised*)
Current:			
Federal	$ (200)	$ (837)	$ 35,861
State	(690)	3,782	14,329
Foreign	339	518	413
Total current income tax expense (benefit)	(551)	3,463	50,603
Deferred:			
Federal	—	341,728	904
State	—	—	—
Total deferred income tax benefit	—	341,728	904
Total income tax expense (benefit)	$ (551)	$ 345,191	$ 51,507

Our expense (benefit) for income taxes differs from the amount computed by applying the U.S. federal statutory rate to income (loss) before taxes. The sources and tax effects of the differences are as follows (in thousands):

	Year Ended December 31,					
	2021		2020 (as revised*)		2019 (as revised*)	
Pre-tax income (loss)	$ (29,148)		$ (134,552)		$ 338,766	
Statutory rate	(6,121)	21.0%	(28,256)	21.0%	71,141	21.0%
State income tax net of federal benefit	4,278	(14.7)%	(37,705)	28.0%	49,000	14.5%
Foreign	143	(0.5)%	49	0.0%	340	0.1%
Net change in valuation allowance	2,885	(9.9)%	460,898	(342.5)%	(37,314)	(11.0)%
Loss on debt transactions	262	(0.9)%	—	—	9,911	2.9%
Impact from outside basis differences	—	—	—	—	(16,344)	(4.8)%
Tax credits	(23,198)	79.6%	(18,774)	14.0%	(22,296)	(6.6)%
Deferred tax true-up	(24)	0.1%	(206)	0.2%	646	0.2%
Tax rate change	12,838	(44.0)%	(32,951)	24.5%	1,248	0.4%
Non-deductible compensation	5,085	(17.4)%	7,931	(5.9)%	3,361	1.0%
Other non-deductible items	84	(0.3)%	193	(0.1)%	329	0.1%
Stock-based compensation	4,720	(16.2)%	17,435	(13.0)%	(4,837)	(1.4)%
Foreign-derived intangible income benefit	—	—	—	—	(2,071)	(0.6)%
Impacts from Akcea Merger	—	—	(22,032)	16.4%	—	—
Other	(1,503)	5.1%	(1,391)	0.9%	(1,607)	(0.6)%
Effective rate	$ (551)	1.9%	$ 345,191	(256.5)%	$ 51,507	15.2%

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes.

Significant components of our deferred tax assets and liabilities as of December 31, 2021 and 2020 are as follows (in thousands):

	Year Ended December 31,	
	2021	2020 (as revised*)
Deferred Tax Assets:		
Net operating loss carryovers	$ 85,600	$ 83,681
Tax credits	269,538	245,746
Deferred revenue	104,330	124,452
Stock-based compensation	86,611	80,055
Intangible and capital assets	92,542	98,443
Convertible debt	45,681	22,395
Interest expense limitation	6,996	—
Other	15,048	13,402
Total deferred tax assets	$ 706,346	$ 668,174
Deferred Tax Liabilities:		
Fixed assets	(3,303)	(3,611)
Other	(5,270)	(5,808)
Net deferred tax asset	$ 697,773	$ 658,755
Valuation allowance	(697,773)	(658,755)
Total net deferred tax assets and liabilities	$ —	$ —

* We revised our 2020 and 2019 amounts to reflect the simplified convertible instruments accounting guidance, which we adopted retrospectively. Refer to Note 1, *Organization and Significant Accounting Policies*, for further information.

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

Ionis and Akcea filed separate U.S. federal income tax returns from the date of Akcea's IPO in 2017 through October 12, 2020, the date on which we completed the Akcea Merger. As a result of the Akcea Merger, Ionis and Akcea now file a consolidated U.S. federal income tax return, and we now assess our U.S. federal and state valuation allowance requirements on a consolidated basis.

We assessed our valuation allowance requirements and recorded a valuation allowance of $341 million against all of Ionis' U.S. federal net deferred tax assets in the fourth quarter of 2020, due to uncertainties related to our ability to realize the tax benefits associated with these assets. We based this determination largely on Akcea rejoining the Ionis consolidated U.S. federal tax group in the fourth quarter of 2020. Due to Akcea's historical and projected financial statement losses, and the expected negative impact this will have on Ionis' consolidated taxable income, we are uncertain if we will generate sufficient consolidated pre-tax income in future periods to realize the Ionis deferred tax benefits. We also expect that Ionis' pre-tax income in future periods will be lower due to significant investments in research and development associated with our pipeline of wholly owned medicines. We now maintain a valuation allowance against all our consolidated U.S. federal and state net deferred tax assets.

Our valuation allowance increased by $39 million from December 31, 2020 to December 31, 2021. The increase was primarily related to increases in our deferred tax assets for tax credits and convertible debt offset against a decrease in our deferred tax asset for deferred revenue.

At December 31, 2021, we had federal and state, primarily California, tax net operating loss carryforwards of $271.5 million and $333.8 million, respectively. Our federal tax loss carryforwards are available indefinitely. Our California tax loss carryforwards will begin to expire in 2031. At December 31, 2021, we also had federal and California research and development tax credit carryforwards of $225.5 million and $99.7 million, respectively. Our federal research and development tax credit carryforwards will begin to expire in 2034. Our California research and development tax credit carryforwards are available indefinitely.

Utilization of the net operating loss and tax credit carryforwards may be subject to an annual limitation due to the ownership change limitations provided by the Internal Revenue Code of 1986, as amended, and similar state provisions. The annual limitation may result in the expiration of net operating losses and credits before utilization.

We analyze filing positions in all U.S. federal, state and foreign jurisdictions where we file income tax returns, and all open tax years in these jurisdictions to determine if we have any uncertain tax positions on any of our income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize uncertain income tax positions if they have less than 50 percent likelihood of the applicable tax authority sustaining our position.

The following table summarizes our gross unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2021	2020	2019
Beginning balance of unrecognized tax benefits	$ 54,163	$ 69,784	$ 68,301
Decrease for prior period tax positions	(695)	(24,154)	(867)
Increase for prior period tax positions	263	7,023	736
Increase for current period tax positions	1,354	1,510	1,614
Ending balance of unrecognized tax benefits	$ 55,085	$ 54,163	$ 69,784

Included in the balance of unrecognized tax benefits at December 31, 2021, 2020 and 2019 was $6.2 million, $6.4 million and $0.4 million respectively, that if we recognized, 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. During the year ended December 31, 2021 and 2020, we recognized $0.5 million and $0.3 million, respectively, of accrued interest and penalties related to gross unrecognized tax benefits. We did not record any accrued interest and penalties for the years ended December 31, 2019.

We are subject to taxation in the U.S. and various state and foreign jurisdictions. Our tax years for 1999 through 2020 are subject to examination by the U.S. federal, state and foreign tax authorities.

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

6. Collaborative Arrangements and Licensing Agreements

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen’s expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. We and Biogen are currently developing nine investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development to treat people with ALS, SMA, AS, Alzheimer’s disease and Parkinson’s disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through December 2021, we have received more than $3.1 billion from our Biogen collaborations.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. From inception through December 2021, we earned more than $1.6 billion in total revenue under our SPINRAZA collaboration, including nearly $1.2 billion in revenue from SPINRAZA royalties and more than $435 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on net sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Biogen is responsible for all global development, regulatory and commercialization activities and costs for SPINRAZA. We completed our performance obligations under our collaboration in 2016.

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a $25 million upfront payment in the fourth quarter of 2017. In December 2021, we earned a $60 million license fee payment when Biogen exercised its option to license ION306. 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 $555 million in payments if Biogen advances ION306, which includes up to $45 million for the achievement of development milestones, up to $110 million for the achievement of regulatory milestones and up to $400 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 $45 millionfor the initiation of a Phase 3 trial under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined the transaction price to be the $25 million upfront payment we received when we entered into the collaboration. We allocated the transaction price to our single performance obligation. In the fourth quarter of 2019, we completed our R&D services performance obligation under this collaboration. We recognized revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. We completed our performance obligation earlier than we previously estimated, as a result, we recognized $8.3 million of additional revenue in the fourth quarter of 2019.

In the fourth quarter of 2021, we identified another performance obligation upon Biogen’s license of ION306 because the license we granted to Biogen is distinct from our other performance obligations. We recognized the $60 million license fee for ION306 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. Biogen is solely responsible for the costs and expenses related to the development, manufacturing and potential future commercialization of ION306 following the option exercise. We do not have any remaining performance obligations under this collaboration.

Neurology Collaborations

2018 Strategic Neurology

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

In the second quarter of 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at an approximately 25 percent cash premium and $375 million in an upfront payment. We are eligible to receive up to $270 million in milestone payments for each medicine that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales. We are currently advancing nine programs under this collaboration and from inception through December 2021, we have received nearly $1.1 billion in payments under this collaboration. We will achieve the next payment of $7.5 million if Biogen designates or advances another programunder this collaboration.

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

From inception through December 2021, we have included $616 million in payments in the transaction price for our R&D services performance obligation under this collaboration, including $23 million of milestone payments we achieved in 2021 and $11 million of milestone payments we achieved in 2020. These milestone payments did not create new performance obligations because they are part of our original R&D services performance obligation. Therefore, we included these amounts in our transaction price for our R&D services performance obligation in the period we achieved the milestone payment. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation at the end of the contractual term in June 2028.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. We will usually be responsible for drug discovery and early development of antisense medicines and Biogen has the option to license antisense medicines after Phase 2 proof-of-concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing six investigational medicines in development under this collaboration, including a medicine for Parkinson's disease (ION859), three medicines for ALS (tofersen, IONIS-C9$_{Rx}$ and ION541), a medicine for multiple system atrophy (ION464) and a medicine for an undisclosed target. In the fourth quarter of 2018, Biogen exercised its option to license our most advanced ALS medicine, tofersen, our medicine in Phase 3 development for SOD1 ALS. As a result, Biogen is now responsible for global development, regulatory and commercialization activities and costs for tofersen.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed under this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. For each antisense molecule that is chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million in a license fee and milestone payments per program. The $260 million per program consists of approximately $60 million in development milestones, including amounts related to the cost of clinical trials, and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any antisense medicines developed under this collaboration. From inception through December 2021, we have received over $280 million in upfront fees, milestone payments and other payments under this collaboration. We will achieve the next payment of up to $70 million if Biogen licenses a medicine under this collaboration.

At the commencement of our 2013 strategic neurology collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $100 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. In the third quarter of 2019, we updated our estimate of the total effort we expect to expend to satisfy our performance obligation. As a result, we recorded a cumulative catch up adjustment of $16.5 million to decrease revenue in the third quarter of 2019. During 2020, we completed our remaining research and development services and recognized the remaining revenue related to this performance obligation. From inception through the completion of our R&D services performance obligation in 2020, we included $145 million in total payments in the transaction price for our R&D services performance obligation.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter we generated the payment because we did not have any performance obligations for the respective payment. For example, in the second quarter of 2021, we earned a $10 million milestone payment when Biogen advanced ION541, which we recognized in full because we did not have any performance obligations related to this milestone payment.

2012 Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense medicines to treat neurodegenerative diseases. We are responsible for the development of each of the medicines through the completion of the initial Phase 2 clinical study for such medicine. Biogen has the option to license a medicine from each of the programs through the completion of the first Phase 2 study for each program. Under this collaboration, we are currently advancing IONIS-MAPT$_{Rx}$ for Alzheimer's disease and ION582 for AS. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. In the fourth quarter of 2019, Biogen exercised its option to license IONIS-MAPT$_{Rx}$. We are responsible for completing the Phase 1/2 in study patients with mild AD and a one-year long-term extension study. Biogen will have responsibility for global development, regulatory and commercialization activities and costs for IONIS-MAPT$_{Rx}$.

Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $210 million in a license fee and milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. The $210 million per program consists of up to $10 million in development milestone payments, plus a mark-up on the cost estimate of the Phase 1 and 2 studies and up to $130 million in milestone payments if Biogen achieves pre-specified regulatory milestones. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales of any medicines resulting from each of the three programs. From inception through December 2021, we have received $155 million in payments under this collaboration, including $19.5 million we received from Biogen for achieving milestones for advancing IONIS-MAPT$_{Rx}$ during 2020. We will achieve the next payment of $25 million if Biogen advances a medicine under this collaboration.

Under our collaboration, we determined we had a performance obligation to perform R&D services. We allocated $40 million in total payments to the transaction price for our R&D services performance obligation. In the third quarter of 2019, we completed our R&D services performance obligation when we designated a development candidate and Biogen accepted the development candidate. Biogen's decision to accept the development candidate was not within our control. We were recognizing revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. Because Biogen accepted the development candidate earlier than when we were previously estimating, we recognized $6.3 million of accelerated revenue in the third quarter of 2019.

When we commenced development for IONIS-MAPT$_{Rx}$ we identified our development work as a separate performance obligation. We are recognizing our IONIS-MAPT$_{Rx}$ development performance obligation based on the percentage of completion. From inception through December 2021, we have included $57 million in the transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation, including $19.5 million milestone payments we earned from Biogen in 2020 when we advanced IONIS-MAPT$_{Rx}$. We currently estimate we will satisfy our performance obligation in 2022.

In the fourth quarter of 2019, we identified another performance obligation upon Biogen's license of IONIS-MAPT$_{Rx}$ because the license we granted to Biogen is distinct from our other performance obligations. We recognized the $45 million license fee for IONIS-MAPT$_{Rx}$ as revenue at that time because Biogen had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Biogen.

In the fourth quarter of 2021, we earned a $10 million milestone payment when Biogen advanced ION582, which we recognized in full because we did not have any performance obligations related to this milestone payment.

During the years ended December 31, 2021, 2020 and 2019, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Year Ended December 31,		
	2021	**2020**	**2019**
SPINRAZA royalties (commercial revenue)	$ 267.8	$ 286.6	$ 293.0
R&D revenue	161.0	122.0	180.6
Total revenue from our relationship with Biogen	$ 428.8	$ 408.6	$ 473.6
Percentage of total revenue	53%	56%	42%

Our consolidated balance sheet at December 31, 2021 and 2020 included deferred revenue of $407.5 million and $465.8 million, respectively, related to our relationship with Biogen.

Joint Development and Commercialization Arrangement

AstraZeneca

Eplontersen Collaboration

In December 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. We are jointly developing and preparing to commercialize eplontersen with AstraZeneca in the U.S. We granted AstraZeneca exclusive rights to commercialize eplontersen outside the U.S., except certain countries in Latin America. Under the terms of the agreement, we received a $200 million upfront payment. We are eligible to receive up to $485 million in development and approval milestones, and up to $2.9 billion in sales-related milestone payments. The agreement also includes territory-specific development, commercial and medical affairs cost-sharing provisions. In addition, we are eligible to receive up to mid-20 percent royalties for sales in the U.S. and tiered royalties up to the high teens for sales outside the U.S.

We evaluated our eplontersen collaboration under ASC 808 and identified four material components: (i) the license we granted to AstraZeneca in 2021, (ii) the co-development activities that we and AstraZeneca will perform, (iii) the co-commercialization activities that we and AstraZeneca will perform and (iv) the co-medical affairs activities that we and AstraZeneca will perform.

We determined that we had a vendor-customer relationship within the scope of ASC 606 for the license we granted to AstraZeneca and as a result we had one performance obligation. For our sole performance obligation, we determined the transaction price was the $200 million upfront payment we received. We recognized the upfront payment in full in 2021 because we did not have any remaining performance obligations after we delivered the license to AstraZeneca.

We also concluded that the co-development activities, the co-commercialization activities and the co-medical affairs activities are within the scope of ASC 808 because we and AstraZeneca are active participants exposed to the risks and benefits of the activities under the collaboration. AstraZeneca will pay 55 percent of the costs associated with the ongoing global Phase 3 development program. As we will continue to lead the Phase 3 development program, we will recognize as revenue the 55 percent of cost-share funding AstraZeneca is responsible for in the same period we incur the related development expenses. As AstraZeneca is responsible for the majority of the commercial and medical affairs costs in the U.S. and all costs associated with bringing eplontersen to market outside the U.S., we will recognize cost-share funding we receive from AstraZeneca related to these activities as a reduction of our commercial and medical affairs expenses.

We will achieve the next payment of up to $50 million upon the first regulatory approval under this collaboration. Through December 2021, we have generated $200 million in payments under this collaboration.

Research and Development Partners

AstraZeneca

In addition to our collaboration for eplontersen, we have two other collaborations with AstraZeneca. One is focused on the treatment of cardiovascular, renal and metabolic diseases and the other is focused on the treatment of oncology diseases. We and AstraZeneca are currently developing six medicines under these collaborations, including medicines in development to treat people with ATTR amyloidosis, cardiovascular disease, a genetically associated form of kidney disease, NASH and cancer. From inception through December 2021, we have received more than $386 million from our AstraZeneca research and development collaborations.

Cardiovascular, Renal and Metabolic Diseases Collaboration

In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiovascular, renal and metabolic diseases. Under our collaboration, AstraZeneca has licensed five medicines from us. AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for each of the medicines it has licensed from us.

Under the terms of the agreement, we received a $65 million upfront payment. We are eligible to receive license fees and milestone payments of up to more than $5.5 billion as medicines under this collaboration advance, including up to $1.1 billion for the achievement of development milestones, up to $2.9 billion for regulatory milestones and up to $1.5 billion for commercial milestones. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. We will achieve the next payment of $10 million under this collaboration if AstraZeneca advances a medicine under this collaboration. From inception through December 2021, we have received over $282 million in an upfront fee, license fees, milestone payments, and other payments under this collaboration, including $30 million we earned in 2021 when AstraZeneca licensed a target for a metabolic disease and $10 million we earned in 2021 when AstraZeneca advanced a target for a metabolic disease.

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 recognized revenue for our R&D services performance obligation as we performed services based on our effort to satisfy this performance obligation relative to our total effort expected to satisfy our performance obligation. We completed our performance obligation in the fourth quarter of 2021. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. From inception through December 2021, we have included $90 million in payments in the transaction price for our R&D services performance obligation.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. For example, in the fourth quarter of 2021, we earned a $30 million license fee when AstraZeneca licensed a target for a metabolic disease. We recognized the license fee as revenue at that time because AstraZeneca 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 AstraZeneca.

Oncology Collaboration

In December 2012, we entered into a collaboration agreement with AstraZeneca to discover and develop antisense medicines to treat cancer. We and AstraZeneca also established an oncology research program. In 2020, AstraZeneca licensed ION736, an investigational medicine in development targeting FOXP3 for the treatment of cancer. AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for ION736.

Under the terms of this agreement, we received $31 million in upfront payments. We are eligible to receive milestone payments and license fees up to $160 million under this collaboration, including up to $42 million for the achievement of development milestones and up to $105 million for the achievement of regulatory milestones. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through December 2021, we have received over $141 million in upfront fees, milestone payments, and other payments under this oncology collaboration, including $13 million we earned when AstraZeneca licensed ION736 in 2020. We will achieve the next payment of $12 million if AstraZeneca advances ION736 in development.

We completed all of the performance obligations we identified under this collaboration in the first quarter of 2018.

Under this collaboration, we have also generated additional payments that we concluded were not part of other performance obligations discussed above. We recognized each of these payments in full in the respective quarter we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. In 2020, we earned a $13 million license fee when AstraZeneca licensed ION736 because AstraZeneca had full use of the license without any continuing involvement from us.

During the years ended December 31, 2021, 2020 and 2019, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	Year Ended December 31,		
	2021	**2020**	**2019**
R&D revenue	$ 254.6	$ 88.0	$ 28.1
Percentage of total revenue	31%	12%	3%

We did not have any deferred revenue from our relationship with AstraZeneca at December 31, 2021. Our consolidated balance sheet at December 31, 2020 included deferred revenue of $10.0 million from 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 fesomersen, which Bayer licensed. In conjunction with the decision to advance these programs, we received a $75 million payment from Bayer. In October 2019, Bayer decided it would advance fesomersen following positive clinical results. Bayer is now responsible for all global development, regulatory and commercialization activities and costs for the FXI program.

We are eligible to receive up to $385 million in license fees, milestone payments and other payments, including up to $125 million for the achievement of development milestones and up to $110 million for the achievement of sales 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 2021, we have received over $191 million from this collaboration. We will achieve the next payment of $20 million if Bayer initiates a Phase 3 study for the FXI program.

At the commencement of this collaboration, we identified three performance obligations, the license of IONIS-FXI$_{Rx}$, R&D services and delivery of API, all of which we completed in 2016.

In February 2017, when we amended our collaboration with Bayer, we identified two new performance obligations, one for the license of fesomersen 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 fesomersen based on its estimated relative stand-alone selling price and recognized the associated revenue upon our delivery of the license in the first quarter of 2017. We allocated $10.1 million to our R&D services performance obligation based on an estimated relative stand-alone selling price. We recognized revenue for our R&D services performance obligation as we performed services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We completed our obligation in the third quarter of 2019.

In the fourth quarter of 2019, we earned a $10 million milestone payment when Bayer decided it would advance fesomersen. We recognized this milestone payment in full in the fourth quarter of 2019 because we did not have any performance obligations related to this milestone payment.

During the years ended December 31, 2021, 2020 and 2019, we earned the following revenue from our relationship with Bayer (in millions, except percentage amounts):

	Year Ended December 31,		
	2021	**2020**	**2019**
R&D revenue	$ 1.1	$ 3.2	$ 14.3
Percentage of total revenue	0%	0%	1%

Our consolidated balance sheet at December 31, 2021 included an insignificant amount of deferred revenue related to our relationship with Bayer. We did not have any deferred revenue from our relationship with Bayer at December 31, 2020.

GSK

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

Under our agreement, if GSK successfully develops these medicines and achieves pre-agreed sales targets, we could receive license fees and milestone payments of more than $260 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 sales 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 2021, we have received more than $190 million in payments under this alliance with GSK. We will achieve the next payment of $15 million if GSK initiates a Phase 3 study of a medicine under this program.

We completed our R&D services performance obligations under our collaboration in the first quarter of 2015. We identified a new performance obligation when we granted GSK the license of the HBV program and assigned related intellectual property rights in the third quarter of 2019 because the license was distinct from our other performance obligations. We recognized the $25 million license fee for the HBV program as revenue at that time because GSK had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to GSK.

We do not have any remaining performance obligations under our collaboration with GSK; however, we can still earn additional payments and royalties as GSK advances the HBV program.

During the years ended December 31, 2021, 2020 and 2019, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	Year Ended December 31,		
	2021	2020	2019
R&D revenue	$ —	$ 0.2	$ 25.4
Percentage of total revenue	—	0%	2%

We did not have any deferred revenue from our relationship with GSK at December 31, 2021 and 2020.

Novartis

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

Under the collaboration, we are eligible to receive up to $675 million in milestone payments, including $25 million for the achievement of a development milestone, up to $290 million for the achievement of regulatory milestones and up to $360 million for the achievement of sales milestones. From inception through December 2021, we have received nearly $425 million in upfront payments, milestone payments, license fees and other payments from this collaboration. We are also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of pelacarsen. In August 2021, we earned a $25 million milestone payment from Novartis when Novartis achieved 50 percent enrollment in the Lp(a) HORIZON Phase 3 cardiovascular outcome study of pelacarsen. We recognized the milestone payment in full in the third quarter of 2021 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of up to $75 million if Novartis advances regulatory activities for pelacarsen.

In conjunction with this collaboration, we entered into a SPA with Novartis. As part of the SPA, Novartis purchased 1.6 million shares of our common stock for $100 million in the first quarter of 2017.

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

- R&D services for pelacarsen;
- R&D services for olezarsen;
- API for pelacarsen; and
- API for olezarsen.

We determined that the R&D services for each medicine and the API for each medicine were distinct performance obligations.

We determined our transaction price to be $108.4 million, comprised of the following:

- $75 million from the upfront payment;
- $28.4 million for the premium paid by Novartis for its purchase of our common stock at a premium in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis would have paid if they purchased our common stock in the future.

We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $64.0 million for the R&D services for pelacarsen;
- $40.1 million for the R&D services for olezarsen;
- $1.5 million for the delivery of pelacarsen API; and
- $2.8 million for the delivery of olezarsen API.

We completed our R&D services performance obligations for olezarsen and pelacarsen in 2019. As such, we recognized all revenue we allocated to the olezarsen and pelacarsen R&D services as of the end of 2019.

We recognized revenue related to the R&D services for pelacarsen and olezarsen performance obligations as we performed services based on our effort to satisfy our performance obligations relative to our total effort expected to satisfy our performance obligations.

During the years ended December 31, 2021, 2020 and 2019, we earned the following revenue from our relationship with Novartis (in millions, except percentage amounts):

	Year Ended December 31,		
	2021	**2020**	**2019**
R&D revenue	$ 25.5	$ 1.0	$ 187.4
Percentage of total revenue	3%	0%	17%

We did not have any deferred revenue from our relationship with Novartis at December 31, 2021 and 2020.

Roche

Huntington's Disease

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

Under the terms of the agreement, we received an upfront payment of $30 million in April 2013 and an additional $3 million payment in 2017. We are eligible to receive up to $365 million in a license fee and milestone payments including up to $70 million for the achievement of development milestones, up to $170 million for the achievement of regulatory milestones and up to $80 million for the achievement of sales 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 net sales of any product resulting from this alliance. From inception through December 2021, we have received $150 million in upfront fees, milestone payments and license fees under this collaboration. We will achieve the next payment of $15 million if Roche advances tominersen into registration.

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

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter in which we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. In 2019, we earned $35 million in milestone payments when Roche dosed the first patient in the Phase 3 study of tominersen.

In January 2022, Roche announced it is actively preparing to initiate a new Phase 2 study of tominersen in patients with HD. Post-hoc analyses from the GENERATION HD1 study suggested tominersen may benefit younger adult patients with lower disease burden. In March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest HD based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded iDMC. We do not have any remaining performance obligations related to tominersen under this collaboration with Roche; however, we can still earn additional payments and royalties as Roche advances tominersen.

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

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

Under the terms of this agreement, we received a $75 million upfront payment in the fourth quarter of 2018. We are eligible to receive more than $680 million in development, regulatory and sales milestone payments and license fees. In addition, we are also eligible to receive tiered royalties from the high teens to 20 percent on net sales. From inception through December 2021, we have received $75 million in upfront fees, milestone payments and license fees under this collaboration. We will achieve the next payment of $20 million if we further advance the Phase 2 study in patients with dry AMD.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. We determined the transaction price to be the $75 million upfront payment we received and allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. During the fourth quarter of 2020, we updated our estimate of the total effort we expected to expend to satisfy our performance obligation under this collaboration. In the fourth quarter of 2020, we recorded a cumulative catch up adjustment of $9.2 million to decrease revenue because we updated our total cost estimate to complete the Phase 2 study of IONIS-FB-L_{Rx} for the treatment of patients with GA. We currently estimate we will satisfy our performance obligation in the fourth quarter of 2023.

During the years ended December 31, 2021, 2020 and 2019, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Year Ended December 31,		
	2021	**2020**	**2019**
R&D revenue	$ 17.2	$ 5.9	$ 57.0
Percentage of total revenue	2%	1%	5%

Our consolidated balance sheet at December 31, 2021 and 2020 included deferred revenue of $31.6 million and $47.2 million related to our relationship with Roche, respectively.

Commercialization Partnerships

Swedish Orphan Biovitrum AB (Sobi)

We began commercializing TEGSEDI and WAYLIVRA in Europe in January 2021 and TEGSEDI in North America in April 2021 through distribution agreements with Sobi. Under our agreements, we are responsible for supplying finished goods inventory to Sobi and Sobi is responsible for selling each medicine to the end customer. In exchange, we earn a distribution fee on net sales from Sobi for each medicine.

PTC Therapeutics

In August 2018, we entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. Under the license agreement, we are eligible to receive royalties from PTC in the mid-20 percent range on net sales for each medicine. In December 2021, we started receiving royalties from PTC for TEGSEDI sales.

Technology Enhancement Collaboration

Bicycle License Agreement

In December 2020, we entered into a collaboration agreement with Bicycle and obtained an option to license its peptide technology to potentially increase the delivery capabilities of our LICA medicines. In July 2021, we paid $42 million when we exercised our option to license Bicycle's technology, which included an equity investment in Bicycle. As part of our stock purchase, we entered into a lockup agreement with Bicycle that restricts our ability to trade our Bicycle shares for one year. In 2021, we recorded a $7.2 million equity investment for the shares we received in Bicycle. We recognized the remaining $34.8 million as R&D expense in 2021. From inception through December 31, 2021, we have paid Bicycle $46.6 million under this collaboration agreement.

Other Agreements

Alnylam Pharmaceuticals, Inc.

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

In the fourth quarter 2020, we completed an arbitration process with Alnylam. The arbitration panel awarded us $41.2 million for payments owed to us by Alnylam related to Alnylam's agreement with Sanofi Genzyme. We recognized the $41.2 million payment from Alnylam as revenue in the fourth quarter of 2020 because we did not have any performance obligations for the respective payment.

During the years ended December 31, 2021, 2020 and 2019, we earned the following revenue from our relationship with Alnylam (in millions, except percentage amounts):

	Year Ended December 31,		
	2021	**2020**	**2019**
R&D revenue	$ —	$ 47.9	$ 24.1
Percentage of total revenue	—	7%	2%

We did not have any deferred revenue from our relationship with Alnylam at December 31, 2021 and 2020.

7. Akcea Merger

Purchase Price and Direct Transaction Costs Accounting for the Akcea Merger

In October 2020, we reacquired the shares of Akcea's common stock we did not own, increasing our ownership from 76 percent to 100 percent. Under the purchase agreement, we purchased 24.8 million shares at $18.15 per share, resulting in a total purchase price of $450.6 million.

To reflect our 100 percent ownership, we accounted for the increase in our ownership by eliminating the noncontrolling interest adjustment in stockholders' equity in accordance with the Consolidation accounting guidance (ASC Topic 810). We recognized the difference between the purchase price and the adjustment to noncontrolling interest in stockholders' equity as additional-paid-in capital. Refer to our *Statement of Stockholders' Equity* for detailed amounts.

We accounted for the transaction costs related to the Akcea Merger as a direct charge to stockholders' equity. We incurred $40.6 million of direct transaction costs from the Akcea Merger, primarily comprised of banking and legal fees.

Equity Award Payouts related to the Akcea Merger

In October 2020, as part of the Akcea Merger, Ionis cancelled all of Akcea's equity awards. In exchange for the cancelled awards, if eligible under the terms of the Akcea Merger, we paid holder's a cash payment. We paid $18.15 for each outstanding RSU. For each outstanding option with an exercise price less than $18.15, we paid $18.15 less the exercise price. As a result, we paid out $53.4 million in the fourth quarter of 2020 related to Akcea's cancelled equity awards. We accounted for these payments as part of the transaction costs recorded to stockholders' equity in the fourth quarter of 2020. Because we did not replace the Akcea awards, we recognized all unrecognized non-cash stock-based compensation ($59.3 million) under Akcea's Plan in our statement of operations in the post-merger period in the fourth quarter of 2020.

Severance and Retention Costs related to the Akcea Merger

As a result of the Akcea Merger, we incurred severance and retention expenses of $27.0 million. During 2021 and 2020, we recorded $11.7 million and $15.3 million of severance and retention related costs in operating expenses, respectively. As of December 31, 2021, we have recognized all severance and retention costs related to the Akcea Merger.

The following table summarizes the severance and retention expenses related to the Akcea Merger that we recognized for the periods indicated (in millions):

	Year Ended December 31, 2021	Year Ended December 31, 2020
R&D expenses	$ 5.1	$ 3.9
SG&A expenses	6.6	11.4
Total	$ 11.7	$ 15.3

The following table summarizes the severance and retention reserve amounts related to the Akcea Merger that we included in accrued compensation for the period indicated (in millions):

	Year Ended December 31, 2021
Beginning balance as of January 1, 2021	$ 14.7
Amount expensed during the year	13.5
Reserve adjustments during the year	(1.8)
Net amount expensed during the year	11.7
Amounts paid during the year	(26.4)
Ending balance as of December 31, 2021	$ —

The reserve adjustments during the period primarily related to forfeitures of severance and retention payments as a result of employee terminations before they earned the amounts.

8. Severance and Retention Costs related to our Restructured Operations

Restructured European Operations

In the fourth quarter of 2020, we entered into a distribution agreement with Sobi to commercialize TEGSEDI and WAYLIVRA in Europe. Under the distribution agreement, Sobi took over all material distribution operations at the end of January 2021. We remain the marketing authorization holder for TEGSEDI and WAYLIVRA in Europe. We will continue to maintain limited European operations including regulatory, manufacturing, and the management of relationships with key opinion leaders. We will also continue to lead the TEGSEDI and WAYLIVRA global commercial strategy.

As a result of this change, we incurred severance and retention expenses of $14.2 million. During 2021 and 2020, we recorded $1.7 million and $12.5 million of severance and retention related costs in operating expenses, respectively. As of December 31, 2021, we have recognized all severance and retention costs related to this agreement.

The following table summarizes the severance and retention expenses related to our restructured European operations that we recognized for the periods indicated (in millions):

	Year Ended December 31, 2021	Year Ended December 31, 2020
R&D expenses	$ 0.6	$ 4.2
SG&A expenses	1.1	8.3
Total	$ 1.7	$ 12.5

The following table summarizes the severance and retention reserve amounts related to our restructured European operations that we included in accrued compensation for the period indicated (in millions):

	Year Ended December 31, 2021
Beginning balance as of January 1, 2021	$ 12.4
Amount expensed during the year	2.6
Reserve adjustments during the year	(0.9)
Net amount expensed during the year	1.7
Amounts paid during the year	(14.1)
Ending balance as of December 31, 2021	$ —

The reserve adjustments during the period primarily related to tax expense adjustments.

Restructured North American TEGSEDI Operations

In April 2021, we entered into a distribution agreement with Sobi for TEGSEDI in North America. Under the terms of the distribution agreement, we will retain the marketing authorizations for TEGSEDI in the U.S. and Canada. We will continue to supply commercial product to Sobi and manage regulatory and manufacturing processes, as well as relationships with key opinion leaders. We will also continue to lead the TEGSEDI global commercial strategy. Sobi will otherwise have responsibility for commercializing TEGSEDI in the U.S. and Canada.

In connection with restructuring our North American TEGSEDI operations, or Restructured North American TEGSEDI Operations, we enacted a plan to reorganize our Akcea workforce in North America to better align with the needs of our business and to focus on our wholly owned pipeline.

The following table summarizes the severance expenses related to our Restructured North American TEGSEDI Operations that we recognized for the period indicated (in millions):

	Year Ended December 31, 2021
R&D expenses	$ 2.3
SG&A expenses	7.1
Total	$ 9.4

We recognized all severance expenses related to our Restructured North American TEGSEDI Operations during the three months ended June 30, 2021.

The following table summarizes the severance reserve amounts related to our Restructured North American TEGSEDI Operations that we included in accrued compensation for the period indicated (in millions):

	Year Ended December 31, 2021
Beginning balance as of January 1, 2021	$ —
Net amount expensed during the year	9.4
Amounts paid during the year	(9.4)
Ending balance as of December 31, 2021	$ —

9. Employment Benefits

We have employee 401(k) salary deferral plans covering all employees. Employees could make contributions by withholding a percentage of their salary up to the IRS annual limits of $20,500 and $27,000 in 2021 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $5.5 million, $5.7 million and $6.4 million in matching contributions for the years ended December 31, 2021, 2020 and 2019, respectively.

10. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If the potential loss from any legal proceeding is considered probable and the amount can be reasonably estimated, we accrue a liability for the estimated loss. Significant judgment is required to determine the probability of a loss and whether the amount of the loss is reasonably estimable. The outcome of any proceeding is not determinable in advance. As a result, the assessment of a potential liability and the amount of accruals recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding, and may revise our estimates.

On August 5, 2021, four purported former stockholders of Akcea filed an action in the Delaware Court of Chancery captioned John Makris, et al. v. Ionis Pharmaceuticals, Inc., et al., C.A. No. 2021-0681, or the “Delaware Action.” The plaintiffs in the Delaware Action assert claims against (i) former members of Akcea’s board of directors; and (ii) Ionis, or collectively, the “Defendants.” The plaintiffs assert putatively direct claims on behalf of a purported class of former Akcea stockholders. The plaintiffs in the Delaware Action assert that the Defendants breached their fiduciary duties in connection with the October 2020 take-private transaction that we and Akcea entered into, in which Akcea became a wholly-owned subsidiary of Ionis. We believe that the claims asserted in the Delaware Action are without merit and filed a motion to dismiss the claims in November 2021. Briefing on the motion to dismiss is ongoing, and pursuant to an agreed-upon scheduling order that has been entered by the Court, argument on the motion to dismiss is expected later in the first quarter of 2022.

On January 19, 2022, a purported stockholder of Ionis filed a stockholder derivative complaint in the Delaware Court of Chancery captioned Leo Shumacher, et al. v. Joseph Loscalzo, et al., C.A. No. 2022-0059, or the “Action.” The complaint names as defendants the current members of Ionis’ board of directors, collectively the Directors. The company is a nominal defendant. Plaintiff asserts a breach of fiduciary duty claim against the Directors for awarding and receiving allegedly excessive compensation. Plaintiff also asserts an unjust enrichment claim against the non-employee Directors as a result of the compensation they received. The complaint seeks, among other things, damages, restitution, attorneys’ fees and costs, and such other relief as deemed just and proper by the court. Defendants have not yet responded to the complaint in this Action.

11. Fourth Quarter Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized fourth quarter data for 2021 and 2020 are as follows (in thousands, except per share data).

Three Months Ended December 31,	2021	2020
Revenue	$ 440,006	$ 290,281
Operating expenses	$ 219,403	$ 312,945
Income (loss) from operations	$ 220,603	$ (22,664)
Net income (loss)	$ 224,613	$ (355,687)
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$ 224,613	$ (354,532)
Basic net income (loss) per share (1) (2)	$ 1.59	$ (2.54)
Diluted net income (loss) per share (1) (3)	$ 1.41	$ (2.54)

(1) We compute net income (loss) per share independently for each quarter during the year.

(2) As discussed in Note 1, *Organization and Significant Accounting Policies*, we compute basic net income (loss) per share by dividing the total net income (loss) attributable to our common stockholders by our weighted-average number of common shares outstanding during the period. Our basic net income per share for the fourth quarter of 2021 was $1.59.

Our basic net loss per share calculation for the fourth quarter of 2020 considered our net loss for Ionis on a stand-alone basis plus our share of Akcea's net loss for the period. To calculate the portion of Akcea's net loss attributable to our ownership, we multiplied Akcea's loss per share by the weighted average shares we owned in Akcea during the period. As a result of this calculation, our total net loss available to Ionis common stockholders for the calculation of net loss per share is different than net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders in the consolidated statements of operations.

Our basic net loss per share for the fourth quarter of 2020 was calculated as follows (in thousands, except per share amounts):

Three Months Ended December 31, 2020	Weighted Average Shares Owned in Akcea	Akcea's Net Loss Per Share	Basic Net Loss Per Share Calculation
Akcea's net loss in the pre-merger period attributable to our ownership	77,095	$ (0.05)	$ (3,603)
Akcea's net loss in the post-merger period attributable to our ownership			(85,987)
Akcea's total net loss attributable to our ownership			$ (89,590)
Ionis' stand-alone net loss			(266,418)
Net loss available to Ionis common stockholders			$ (356,008)
Weighted average shares outstanding			139,956
Basic net loss per share			$ (2.54)

(3) We had net income available to Ionis common stockholders for the fourth quarter of 2021. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period as follows (in thousands except per share amounts):

Three Months Ended December 31, 2021	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$ 224,612	141,205	$ 1.59
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	46	
Shares issuable upon restricted stock award issuance	—	1,065	
Shares issuable related to our ESPP	—	34	
Shares issuable related to our 0 percent convertible notes	777	10,936	
Shares issuable related to our 0.125 percent convertible notes	716	6,590	
Shares issuable related to our 1 percent convertible notes	105	464	
Income available to Ionis common stockholders, plus assumed conversions	$ 226,210	160,340	$ 1.41

Exhibit 4.11

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

As of December 31, 2021, Ionis Pharmaceuticals, Inc. (the "Company") had one class of securities, its Common Stock, registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act").

Description of Common Stock

General

The following description of our Common Stock is a summary and does not purport to be complete. It is subject to and qualified in its entirety by reference to our Amended and Restated Certificate of Incorporation, as amended (the "Certificate of Incorporation"), and our Amended and Restated Bylaws (the "Bylaws"), each of which are incorporated by reference as an exhibit to the Annual Report on Form 10-K of which this Exhibit 4.11 is a part. We encourage you to read our Certificate of Incorporation, Bylaws and the applicable provisions of the General Corporation Law of Delaware (the "DGCL") for additional information.

Authorized Capital Stock

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

Voting Rights

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

Dividend Rights

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

Classification of the Board of Directors

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

Liquidation, Dissolution or Winding Up

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

Other Rights and Preferences

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

Anti-Takeover Provisions

Delaware Anti-takeover Law

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

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

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

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

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

Certificate of Incorporation and Bylaws Provisions

Our Certificate of Incorporation includes a provision that requires at least 66-2/3% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

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

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

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

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

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

- classifies our board of directors into three classes;

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

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

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

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

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

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

Choice of Forum

Our Bylaws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery does not have jurisdiction, another state court located within the State of Delaware or, if no state court located within the State of Delaware has jurisdiction, the federal district court for the District of Delaware) shall, to the fullest extent permitted by law, be the sole and exclusive forum for (i) any derivative claim or cause of action or proceeding brought on behalf of the Company; (ii) any claim or cause of action for breach of a fiduciary duty owed by any current or former director, officer or other employee of the Company to the Company or the Company's stockholders; (iii) any claim or cause of action against the Company or any current or former director or officer or other employee of the Company arising out of or pursuant to any provision of the DGCL, our Certificate of Incorporation (as may be amended from time to time) or our Bylaws (as may be amended from time to time); and (iv) any action asserting a claim against the Company or any current or former director or officer or other employee of the Company governed by the internal affairs doctrine; (v) any claim or cause of action seeking to interpret, apply, enforce or determine the validity of the Bylaws or the Certificate of Incorporation of the corporation (as each may be amended from time to time, including any right, obligation, or remedy thereunder); and (vi) any claim or cause of action as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware, in all cases to the fullest extent permitted by law and subject to the court having personal jurisdiction over the indispensable parties named as defendants. This choice of forum provision does not apply to claims or causes of action brought to enforce a duty or liability created by the Securities Act of 1933, as amended, or the Exchange Act, as amended, or any other claim for which the federal courts have exclusive jurisdiction. Any person or entity purchasing or otherwise acquiring any interest in shares of capital stock of the Company shall be deemed to have notice of and consented to the provisions of Article XV of the Bylaws.

Exhibit 10.19

IONIS PHARMACEUTICALS, INC.
PERFORMANCE BASED RESTRICTED STOCK UNIT GRANT NOTICE
(2011 EQUITY INCENTIVE PLAN)

Ionis Pharmaceuticals, Inc. (the ***"Company"***), pursuant to its Amended and Restated 2011 Equity Incentive Plan (the ***"Plan"***), hereby awards to Participant a Performance Based Restricted Stock Unit (***"PRSU"***) Award for the number of stock units set forth below (the ***"Award"***). The Award is subject to all of the terms and conditions as set forth herein; and in the Plan and the Performance Based Restricted Stock Unit Agreement (the ***"Agreement"***), both of which are attached hereto and incorporated herein in their entirety. Capitalized terms not otherwise defined herein shall have the meanings set forth in the Plan or the Agreement. In the event of any conflict between the terms in the Award and the Plan, the terms of the Plan shall control.

Participant:	
Date of Grant:	
Target Number of Stock Units Subject to Award:	
Maximum Number of Stock Units Subject to Award:	
Consideration:	Participant's Services

Vesting Schedule: Subject to Section 4(b) of the Agreement, if Participant ceases to be a Service Provider for any or no reason before Participant vests in the PRSU, the PRSU and Participant's right to acquire any Shares hereunder will immediately terminate.

Up to one third (1/3) of the maximum number of PRSUs subject to the Agreement are eligible for vesting at the end of each Performance Period depending on the Company's relative Total Shareholder Return over the applicable Performance Periods, but subject to the Alternative Three Year Performance Period Vested Unit Calculation (each as more fully described in the PRSU Agreement).

You must accept this Award prior to the first vesting date. If you do not accept this Award by the first vest date, this Award will automatically expire.

Issuance Schedule: The shares of Common Stock to be issued in respect of the Award will be issued in accordance with Section 1 of the Agreement.

Special Tax Withholding Right: *If permitted by the Company*, you may direct the Company (i) to withhold, from shares otherwise issuable in respect of the Award, a portion of those shares with an aggregate fair market value (measured as of the delivery date) equal to the amount of the applicable withholding taxes, and (ii) to make a cash payment equal to such fair market value directly to the appropriate taxing authorities, as provided in Section 12 of the Agreement.

Additional Terms/Acknowledgements: The undersigned Participant acknowledges receipt of, and understands and agrees to, this Grant Notice, the Agreement and the Plan. Participant further acknowledges that as of the Date of Grant, this Grant Notice, the Agreement and the Plan set forth the entire understanding between Participant and the Company regarding the Award and supersede all prior oral and written agreements on that subject, with the exception of any employment or severance arrangement that would provide for vesting acceleration of the Award upon the terms and conditions set forth therein.

IONIS PHARMACEUTICALS, INC.

By: _____
Signature

Title: _____

Date: _____

PARTICIPANT:

_____
Signature

Date: _____

ATTACHMENTS: Performance Based Restricted Stock Unit Agreement

IONIS PHARMACEUTICALS, INC.
AMENDED & RESTATED 2011 EQUITY INCENTIVE PLAN

PERFORMANCE BASED RESTRICTED STOCK UNIT AGREEMENT

Pursuant to the Performance Based Restricted Stock Unit Grant Notice ("***Grant Notice***") and this Performance Based Restricted Stock Unit Agreement ("***Agreement***") and in consideration of your services, Ionis Pharmaceuticals, Inc. (the "***Company***") has awarded you a Performance Based Restricted Stock Unit Award (the "***Award***") under its Amended & Restated 2011 Equity Incentive Plan (the "***Plan***"). Your Award is granted to you effective as of the Date of Grant set forth in the Grant Notice for this Award. This Agreement will be deemed to be agreed to by the Company and you upon the earlier of (i) signing (or electronic acceptance) by you of the Grant Notice to which it is attached, and (ii) your receipt of shares of Common Stock under this Agreement. Capitalized terms not explicitly defined in this Agreement will have the same meanings given to them in the Plan or the Grant Notice, as applicable. In the event of any conflict between the terms in this Agreement and the Plan, the terms of the Plan will control. The details of your Award, in addition to those set forth in the Grant Notice and the Plan, are as follows.

1. GRANT AND VESTING OF THE AWARD.

(a) This Award represents the right to be issued on a future date the number of shares of the Company's Common Stock that is equal to the number of performance based restricted stock units ("***PRSUs***") as described below. This Award was granted in consideration of your services to the Company. Except as otherwise provided herein, you will not be required to make any payment to the Company (other than past and future services to the Company) with respect to your receipt of the Award, the vesting of the PRSUs or the delivery of the Common Stock to be issued in respect of the Award.

(b) One third (1/3) of the maximum number of PRSUs subject to this Agreement are eligible for vesting at the end of each Performance Period depending on the Company's relative Total Shareholder Return over the applicable Performance Period, but *subject to* the Alternative Three Year Performance Period Vested Unit Calculation (each as more fully described below).

(c) Following the end of each Performance Period, the Company's Compensation Committee (the "***Committee***") will certify the Company's relative Total Shareholder Return on a percentage rank basis compared to the Comparison Group (the "***Performance Measure***") for such Performance Period (the "***Certification***"). The PRSUs subject to vesting during a Performance Period will be subject to forfeiture and cancellation by the Company if the Company's performance during such Performance Period does not meet or exceed the Threshold Level (as defined in the table set forth in Section 3(a)(iii)) of the Performance Measure for such Performance Period; *provided however*, that such forfeited shares may be subsequently granted subject to the Alternative Three Year Performance Period Vested Unit Calculation. Performance at or above the Threshold Level will result in PRSUs becoming vested as set forth below, and shares underlying such vested PRSUs will be promptly distributed following completion of the Certification but in no event later than March 15 of the year following the year in which the applicable Certification occurred.

(d) Notwithstanding the foregoing, following completion of the three-year period commencing on the Date of Grant and ending on the third anniversary of the Date of Grant (the "***Three Year Performance Period***"), the Committee will determine the number of PRSUs that would vest if the maximum number of PRSUs subject to the Award had been subject only to the Three Year Performance Period (the "***Alternative Three Year Performance Period Vested Unit Calculation***"). If the number of PRSUs that vest pursuant to the Alternative Three Year Performance Period Vested Unit Calculation is greater than the number of PRSUs that vest under this Agreement in the three Performance Periods described herein without regard to the Alternative Three Year Performance Period Vested Unit Calculation, then such greater number of PRSUs will vest pursuant to the Alternative Three Year Performance Period Vested Unit Calculation, reduced by the number of PRSUs previously vested.

2. ADDITIONAL DEFINITIONS.

(a) "***Comparison Group***" means the companies included in the NASDAQ Biotechnology Index on the Date of Grant, as may be adjusted as described in Section 3(b)(iii) below.

(b) "***Performance Period***" means each of the following three periods:

(i) the one-year period commencing on the Date of Grant and ending on the first anniversary of the Date of Grant;

(ii) the two-year period commencing on the Date of Grant and ending on the second anniversary of the Date of Grant; and

(iii) the three-year period commencing on the Date of Grant and ending on the third anniversary of the Date of Grant.

(c) "***Target***" means the target number of shares set forth in the Grant Notice. The Target for each Performance Period will be one-third of the target number of shares set forth in the Grant Notice.

(d) "***Total Shareholder Return***" or "***TSR***" means total shareholder return as applied to the Company or any company in the Comparison Group, meaning stock price appreciation from the beginning to the end of the applicable Performance Period, plus dividends and distributions made or declared (assuming such dividends or distributions are reinvested in the common stock of the Company or any company in the Comparison Group) during the Performance Period, expressed as a percentage return.

3. CALCULATION.

(a) For purposes of the Award, subject to the Negative TSR Cap set forth in Section 3(b)(i) below, the number of PRSUs earned at the end of each Performance Period will be calculated using the method as follows:

(i) First, for the Company and for each other company in the Comparison Group, determine the TSR for the Performance Period.

(ii) Next, rank the TSR values determined in step (i) above from low to high (with the company having the lowest TSR being ranked number 1, the company with the second lowest TSR ranked number 2, and so on) and determine the Company's percentile rank based upon its position in the list by dividing the Company's position by the total number of companies (including the Company) in the Comparison Group and rounding the quotient to the nearest hundredth. For example, if the Company was ranked 61 on the list out of 80 companies (including the Company), its percentile rank would be 76.25%.

(iii) Finally, plot the percentile rank for the Company determined in accordance with step (ii) above into the appropriate band in the left-hand column of the table below to determine the number of shares earned as a percent of the applicable Target for the applicable Performance Period, which is the figure in the right-hand column of the table below corresponding to that percentile rank. Use linear interpolation between points in the table below to determine the percentile rank and the corresponding share funding if the Company's percentile rank is greater than 25% and less than 75% but not exactly one of the percentile ranks listed in the left-hand column.

	TSR Percentile Rank	**Shares Earned as a Percent of Target**
Maximum Level	75%	150%
	70%	140%
	65%	130%
	60%	120%
	55%	110%
Target Level	50%	100%
	45%	90%
	40%	80%
	35%	70%
	30%	60%
Threshold Level	25%	50%

There is no minimum number of shares or other consideration that you will receive, and no shares will be earned, if the percentile rank is below the 25th percentile in a Performance Period.

(b) Rules of Calculation:

(i) If the Company's absolute TSR is negative over the applicable Performance Period, the pay-out will not exceed 100% of Target for that Performance Period, even if the percentile rank exceeds the 50th percentile (the "***Negative TSR Cap***").

(ii) Except as modified in Section 3(b)(iii) or 3(b)(iv) below, for purposes of computing TSR, the stock price at the beginning of the Performance Period will be the average closing price of a share of common stock over the 20 trading days beginning on the first day of the Performance Period, and the stock price at the end of the Performance Period will be the average closing price of a share of common stock over the 20 trading days preceding and including the last day of the Performance Period, adjusted for changes in capital structure; *provided, however*, that TSR will be negative one hundred percent (-100%) if a company: (A) files for bankruptcy, reorganization, or liquidation under any chapter of the U.S. Bankruptcy Code; (B) is the subject of an involuntary bankruptcy proceeding that is not dismissed within 30 days; (C) is the subject of a stockholder approved plan of liquidation or dissolution; or (D) ceases to conduct substantial business operations.

(iii) Companies will be removed from the Comparison Group if they undergo a Specified Corporate Change. A company that is removed from the Comparison Group before the measurement date will not be included at all in the computation of relative TSR. A company in the Comparison Group will be deemed to have undergone a ***Specified Corporate Change*** *if* it (A) ceases to be a domestically domiciled publicly traded company on a national stock exchange or market system, unless such cessation of such listing is due to a low stock price or low trading volume; (B) has gone private; (C) has reincorporated in a foreign (e.g., non-U.S.) jurisdiction, regardless of whether it is a reporting company in that or another jurisdiction; or (D) has been acquired by another company (whether by a peer company or otherwise, but not including internal reorganizations), or has sold all or substantially all of its assets.

(iv) The Company's Compensation Committee may in its good faith discretion calculate the TSRs and TSR Percentile Rank using a subscription service (such as Bloomberg) provided such calculation is (A) consistently applied, (B) intended to ease the burden of administering this Award, and (C) intended to preserve the overall intent of this Award.

4. VESTING AND TERMINATION OF CONTINUOUS SERVICE.

(a) In General. Subject to the limitations contained herein, your Award will vest, if at all, in accordance with Section 1 above, provided that vesting will cease upon the termination of your Continuous Service except as set forth below. Upon termination of your Continuous Service, the PRSUs that were not vested on the date of such termination will be forfeited at no cost to the Company, and you will have no further right, title or interest in the PRSUs or the shares of Common Stock to be issued in respect of the Award except as set forth below.

(b) Change in Control.

(i) If a Change in Control Termination (as such term is defined in the Company's Severance Benefit Plan adopted October 18, 2018 (the "***Severance Plan***")) occurs during the Change in Control Protection Period (as such term is defined in the Severance Plan), the Award will pay-out at Target and the Target PRSUs subject to such Award that have not already vested will vest immediately upon the Change in Control Termination.

(ii) If a Change in Control (as such term is defined in the Severance Plan) occurs and your Award will not be assumed, continued or substituted by the successor or acquiror entity in such Change in Control, the Award will pay-out at Target and the Target PRSUs subject to such Award that have not already vested will vest immediately upon the Change in Control.

(iii) If a Change in Control (as such term is defined in the Severance Plan) occurs and your Award will be assumed, continued or substituted by the successor or acquiror entity in such Change in Control, the PRSUs subject to such Award will automatically convert upon the Change in Control to time-vested restricted stock units ("***RSUs***") at a rate of one RSU for each of the Target number of PRSUs. The RSUs will not be subject to the relative TSR performance measure described in Section 1 above and instead will vest at Target at the end of the applicable Performance Periods outlined in Section 2(b) above that are still remaining at the time of the Change in Control. Such RSUs will be subject to further acceleration in the case of a Change in Control Termination during the Change in Control Protection Period (as such term is defined in the Severance Plan).

(iv) Notwithstanding anything to the contrary in this Agreement or the Severance Plan, if you are a party to a prior written employment agreement, change of control agreement, or plan or other similar written agreement or plan (each, a "***Prior Agreement***"), that provides, in certain circumstances, for greater benefits regarding the accelerated vesting of equity awards (including PRSUs) following a Change in Control of the Company or similar transaction, the terms of such Prior Agreement shall control the definition of the term "*Change in Control*" (or any term used therein of similar import) and the terms and conditions by which the vesting of the PRSUs may be accelerated as a result of a Change in Control, as well as the benefits that may otherwise be available to you upon a Change in Control.

5. Adjustments to Number of Shares.

(a) The number of PRSUs subject to your Award may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan.

(b) Any additional PRSUs that become subject to the Award pursuant to this Section 5 and Section 9, if any, will be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other PRSUs covered by your Award.

(c) Notwithstanding the provisions of this Section 5, no fractional shares or rights for fractional shares of Common Stock will be created pursuant to this Section 5. The Board will, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 5.

6. Securities Law Compliance. You may not be issued any shares in respect of your Award unless either (i) the shares are registered under the Securities Act; or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award also must comply with other applicable laws and regulations governing the Award, and you will not receive such shares if the Company determines that such receipt would not be in material compliance with such laws and regulations.

7. Transfer Restrictions. Prior to the time that shares of Common Stock have been delivered to you, you may not transfer, pledge, sell or otherwise dispose of this Award or the shares issuable in respect of your Award, except as expressly provided in this Section 7. For example, you may not use shares that may be issued in respect of your Award as security for a loan. The restrictions on transfer set forth herein will lapse upon delivery to you of shares in respect of your vested Award.

(a) Death. Your Award is transferable by will and by the laws of descent and distribution. In addition, upon receiving written permission from the Board or its duly authorized designee, you may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company and any broker designated by the Company to effect transactions under the Plan, designate a third party who, in the event of your death, will thereafter be entitled to receive any distribution of Common Stock or other consideration to which you were entitled at the time of your death pursuant to this Agreement. In the absence of such a designation, your executor or administrator of your estate will be entitled to receive, on behalf of your estate, such Common Stock or other consideration.

(b) Certain Trusts. Upon receiving written permission from the Board or its duly authorized designee, you may transfer your Award to a trust if you are considered to be the sole beneficial owner (determined under Section 671 of the Code and applicable state law) while the Award is held in the trust, provided that you and the trustee enter into transfer and other agreements required by the Company.

(c) Domestic Relations Orders. Upon receiving written permission from the Board or its duly authorized designee, and provided that you and the designated transferee enter into transfer and other agreements required by the Company, you may transfer your Award or your right to receive the distribution of Common Stock or other consideration thereunder, pursuant to a domestic relations order that contains the information required by the Company to effectuate the transfer. You are encouraged to discuss the proposed terms of any division of this Award with the Company prior to finalizing the domestic relations order to help ensure the required information is contained within the domestic relations order.

8. Date of Issuance.

(a) If the Award is exempt from application of Section 409A of the Code and the regulations and other guidance thereunder and any state law of similar effect (collectively ***"Section 409A"***), the Company will deliver to you a number of shares of the Company's Common Stock equal to the number of vested PRSUs subject to your Award, including any additional PRSUs received pursuant to Section 5 above that relate to those vested PRSUs on the applicable vesting date(s). However, if a scheduled delivery date falls on a date that is not a business day, such delivery date will instead fall on the next following business day. Notwithstanding the foregoing, in the event that (i) you are subject to the Company's policy permitting officers and directors to sell shares only during certain "window" periods, in effect from time to time (the "***Policy***") or you are otherwise prohibited from selling shares of the Company's Common Stock in the public market and any shares covered by your Award are scheduled to be delivered on a day (the "***Original Distribution Date***") that does not occur during an open "window period" applicable to you or a day on which you are permitted to sell shares of the Company's Common Stock pursuant to a written plan that meets the requirements of Rule 10b5-1 under the Exchange Act, in each case as determined by the Company in accordance with the Policy, or does not occur on a date when you are otherwise permitted to sell shares of the Company's Common Stock on the open market, and (ii) the Company elects not to satisfy its tax withholding obligations (if any) by withholding shares from your distribution, then such shares will not be delivered on such Original Distribution Date and will instead be delivered on the first business day of the next occurring open "window period" applicable to you pursuant to such policy (regardless of whether you are still providing Continuous Services at such time) or the next business day when you are not prohibited from selling shares of the Company's Common Stock in the open market, but in no event later than the fifteenth day of the third calendar month of the calendar year following the calendar year in which the shares covered by the Award vest. Delivery of the shares pursuant to the provisions of this Section 8(a) is intended to comply with the requirements for the short-term deferral exemption available under Treasury Regulation 1.409A-1(b)(4) and will be construed and administered in such manner. The form of such delivery of the shares (*e.g.*, a stock certificate or electronic entry evidencing such shares) will be determined by the Company.

(b) The provisions of this Section 8(b) are intended to apply if the Award is subject to Section 409A because of the terms of a severance arrangement or other agreement between you and the Company that provides for acceleration of vesting of the Award upon your separation from service (as such term is defined in section 409A(a)(2)(A)(i) of the Code and applicable guidance thereunder ("***Separation From Service***") and such severance benefit does not satisfy the requirements for an exemption from application of Section 409A provided under Treasury Regulations Sections 1.409A-1(b)(4) or 1.409A-1(b)(9) ("***Non-Exempt Severance Arrangement***"). If the Award is subject to and not exempt from application of Section 409A due to application of a Non-Exempt Severance Arrangement, the following provisions in this Section 8(b) will supersede anything to the contrary in Section 8(a).

(i) If the Award vests in ordinary course during your Continuous Service in accordance with the vesting schedule set forth in the Grant Notice, in no event will the shares to be issued in respect of your Award be issued any later than the later of: (A) December 31st of the calendar year that includes the applicable vesting date, or (B) the 60th day that follows the applicable vesting date.

(ii) If the Award accelerates vesting under the terms of your Non-Exempt Severance Arrangement in connection with your Separation From Service, and such vesting acceleration provisions of your Non-Exempt Severance Arrangement were in effect as of the Date of Grant of the Award and therefore part of the terms of the Award as of the Date of Grant, then the shares will be earlier issued in respect of your Award upon your Separation From Service in accordance with the terms of the Non-Exempt Severance Arrangement, but in no event later than the 60th day that follows the date of your Separation From Service. However, if at the time the shares would otherwise be issued you are subject to the distribution limitations contained in section 409A of the Code applicable to "specified employees" as defined in section 409A(a)(2)(B)(i) of the Code and applicable guidance thereunder, such share issuances will not be made before the date which is six months following the date of your Separation From Service, or, if earlier, the date of your death that occurs within such six month period.

(iii) If the Award accelerates vesting under the terms of your Non-Exempt Severance Arrangement in connection with your Separation From Service, and such vesting acceleration provisions of your Non-Exempt Severance Arrangement were not in effect as of the Date of Grant of the Award and therefore not a part of the terms of the Award on the Date of Grant, then such acceleration of vesting of the Award will not accelerate the issuance date of the shares, but the shares will instead be issued on the same schedule as set forth on the Grant Notice as if they had vested in ordinary course during your Continuous Service, notwithstanding the vesting acceleration of the Award. Such issuance schedule is intended to satisfy the requirements of payment on a specified date or pursuant to a fixed schedule, as provided under Treas. Reg. 1.409A-3(a)(4).

(c) The provisions in this Agreement for delivery of the shares in respect of the Award are intended either to comply with the requirements of Section 409A or to provide a basis for exemption from such requirements so that the delivery of the shares will not trigger the additional tax imposed under Section 409A, and any ambiguities herein will be so interpreted.

9. Dividends. You will be entitled to receive payments equal to any cash dividends and other distributions paid with respect to a corresponding number of shares to be issued in respect of the PRSUs covered by your Award, provided that if any such dividends or distributions are paid in shares, the Fair Market Value of such shares will be converted into additional PRSUs covered by the Award, and further provided that such additional PRSUs will be subject to the same forfeiture restrictions and restrictions on transferability as apply to the PRSUs subject to the Award with respect to which they relate.

10. Restrictive Legends. The shares issued in respect of your Award will be endorsed with appropriate legends determined by the Company.

11. Award not a Service Contract.

(a) Your Continuous Service with the Company or an Affiliate is not for any specified term and may be terminated by you or by the Company or an Affiliate at any time, for any reason, with or without cause and with or without notice. Nothing in this Agreement (including, but not limited to, the vesting of your Award pursuant to Section 1 herein or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Agreement or the Plan will: (i) confer upon you any right to continue in the employ of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or an Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other term or condition of employment or affiliation; (iii) confer any right or benefit under this Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

(b) By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to Section 1 is earned only by continuing as an employee, director or consultant at the will of the Company (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a "reorganization"). You further acknowledge and agree that such a reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule set forth herein or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee or consultant for the term of this Agreement, for any period, or at all, and will not interfere in any way with your right or the Company's right to terminate your Continuous Service at any time, with or without cause and with or without notice.

12. WITHHOLDING OBLIGATIONS.

(a) On or before the time you receive a distribution of shares subject to your Award, or at any time thereafter as requested by the Company, you hereby authorize any required withholding (if any) from the Common Stock issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations (if any) of the Company or any Affiliate which arise in connection with your Award (the "***Withholding Taxes***"). Additionally, the Company may, in its sole discretion, satisfy all or any portion of the Withholding Taxes obligation relating to your Award by any of the following means or by a combination of such means: (i) withholding from any compensation otherwise payable to you by the Company; (ii) causing you to tender a cash payment; or (iii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 8) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Common Stock so withheld will not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

(b) Unless the tax withholding obligations of the Company and/or any Affiliate are satisfied, the Company will have no obligation to deliver to you any Common Stock.

(c) In the event the Company's obligation to withhold arises prior to the delivery to you of Common Stock or it is determined after the delivery of Common Stock to you that the amount of the Company's withholding obligation was greater than the amount withheld by the Company, you agree to indemnify and hold the Company harmless from any failure by the Company to withhold the proper amount.

(d) If specified in your Grant Notice and permitted by the Company, you may direct the Company to withhold shares of Common Stock with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 8) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Common Stock so withheld will not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

13. UNSECURED OBLIGATION. Your Award is unfunded, and as a holder of a vested Award, you will be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares pursuant to this Agreement. You will not have voting or any other rights as a stockholder of the Company with respect to the shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 8 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a stockholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, will create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

14. OTHER DOCUMENTS. You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's insider-trading policy and agree that you may sell shares only in compliance with such policy, in effect from time to time.

15. NOTICES. Any notices provided for in your Award or the Plan will be given in writing and will be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. You hereby consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

16. MISCELLANEOUS.

(a) The rights and obligations of the Company under your Award will be transferable to any one or more persons or entities, and all covenants and agreements hereunder will inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your Award may only be assigned with the prior written consent of the Company.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

(c) You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award, and fully understand all provisions of your Award.

(d) This Agreement will be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Agreement will be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

17. GOVERNING PLAN DOCUMENT. Your Award is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. Except as expressly provided herein, in the event of any conflict between the provisions of your Award and those of the Plan, the provisions of the Plan will control.

18. Severability. If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity will not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid will, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

19. Effect on Other Employee Benefit Plans. The value of the Award subject to this Agreement shall not be included as compensation, earnings, salaries, or other similar terms used when calculating your benefits under any employee benefit plan sponsored by the Company or any Affiliate, except as such plan otherwise expressly provides. The Company expressly reserves its rights to amend, modify, or terminate any of the Company's or any Affiliate's employee benefit plans.

20. Choice of Law. The interpretation, performance and enforcement of this Agreement will be governed by the law of the state of California without regard to such state's conflicts of laws rules.

21. Amendment. This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change will be applicable only to rights relating to that portion of the Award which is then subject to restrictions as provided herein.

22. Discretion of the Committee. Unless otherwise explicitly provided herein, the Compensation Committee of the Board of Directors of the Company, or an authorized successor committee thereto, shall make all determinations required to be made hereunder, including but not limited to determinations relating to the achievement of any thresholds or the vesting of any PRSUs hereunder, and shall interpret all provisions of this PRSU Award Agreement and the underlying PRSUs, as it deems necessary or desirable, in its sole and absolute discretion. Such determinations and interpretations shall be binding on and conclusive to the Company and you. Without limiting the foregoing, the Company may, in its sole and absolute discretion, delay payments hereunder or make such other modifications with respect to the issuance of stock hereunder as it reasonably deems necessary to the extent that (a) audited financials are not complete for any applicable period during the Performance Period and/or (b) the Company has not had an adequate opportunity to review the audited financials or confirm the applicable TSR Percentile Ranks.

Exhibit 10.60

IONIS PHARMACEUTICALS, INC.

FOURTH AMENDED AND RESTATED
STRATEGIC ADVISORY SERVICES AGREEMENT (*"SUMMARY PAGE"*)

This Fourth Amended and Restated Strategic Advisory Services Agreement is entered into by and between Lyme Pinnacle Consulting Inc., for the services of B. Lynne Parshall, and is made effective as of February 22, 2022, and amends and restates the Strategic Advisory Service Agreement dated January 15, 2018, as amended on March 22, 2019, January 9, 2020 and February 22, 2021, by and between B. Lynne Parshall and Ionis Pharmaceuticals, Inc. ("***Ionis***").

Date of Fourth Amended and Restated Strategic Advisory Services Agreement: ("***Agreement***")	February 22, 2022 ("4th ***A&R Effective Date***").
Name of Strategic Advisor:	B. Lynne Parshall (hereinafter "***Strategic Advisor***").
Scope of Strategic Advisory Services:	Provide advisory services to Ionis on projects as directed by the CEO.
Duration of Strategic Advisory Services (the "***Strategic Advisory Period***"):	Commencing January 1, 2022 and continuing through December 31, 2022.
Consideration for Strategic Advisory Services:	Annual fee of $225,000 to be paid quarterly.

In addition to such compensation, Ionis will reimburse Strategic Advisor for Ionis directed travel, lodging and related expenses or reasonable rate equivalents for lodging, car and meals that Strategic Advisor incurs in the course of performing Strategic Advisory Services under this Agreement. All such reimbursements will be in accordance with Ionis' travel policy and Strategic Advisor will provide Ionis with reasonably acceptable supporting documentation.

Strategic Advisor agrees to provide Ionis with Strategic Advisory Services on the terms described above and according to the additional terms attached hereto as Exhibit A. In this Agreement references to Ionis will include Ionis' affiliate companies where applicable.

	Lyme Pinnacle Consulting Inc.	**Ionis Pharmaceuticals, Inc.**
By (Signature):	/s/B. Lynne Parshall	/s/Brett Monia
Date:	February 23, 2022	February 22, 2022
Printed Name:	B. Lynne Parshall, for Lyme Pinnacle Consulting Inc.	Brett Monia

Social Security or Employer Tax ID Number to be provided separately via W-9 form or foreign equivalent.

EXHIBIT A

TERMS OF STRATEGIC ADVISORY AGREEMENT

1. Engagement of Services

Strategic Advisor is retained to perform certain services, as needed and requested by Ionis ("***Strategic Advisory Services***"). Strategic Advisor will perform such Strategic Advisory Services to the best of Strategic Advisor's talent and ability.

2. Compensation

(a) As full and complete compensation for Strategic Advisory Services and for the discharge of all of Strategic Advisor's obligations hereunder, Ionis will pay Strategic Advisor at the annual rate of $225,000 to be paid quarterly in calendar year 2022. Strategic Advisor will submit reimbursable expenses to Ionis electronically, and Ionis, upon its approval, will pay all undisputed fees and expenses within 30 days after Ionis' receipt of the reimbursement request.

(b) *Ionis Stock Awards:*

(i) Since you transitioned seamlessly from an Ionis employee to a nonemployee director, the stock options and RSUs you received for your previous service as an Ionis employee will continue to vest so long as your Continuous Service (as defined in the applicable equity plan) continues.

(ii) Once you are no longer serving on the Ionis board and no longer providing Strategic Advisory Services, to the extent permitted by the terms of the applicable stock option agreement, your vested stock options will not terminate until the earlier of 18 months following your retirement or the expiration of the original term of such stock option.

(iii) For the 18 months following the end of your Ionis board of directors services, if you are eligible for continued health coverage under COBRA, Ionis will pay your COBRA premium payments sufficient to continue your coverage at your then current level, or if COBRA is not available, Ionis will pay you an amount equal to the cost of comparable replacement coverage.

(c) While you are providing Strategic Advisory Services, Ionis will make an appropriate level of administrative and technical personnel available to facilitate your performance of Advisory Services at no cost to you, including, without limitation IT support and access to Ionis' electronic calendar and IT systems that are necessary to perform your duties.

3. Independent Contractor

Strategic Advisor is an independent contractor and not an employee of Ionis. Strategic Advisor has no authority to obligate Ionis by contract or otherwise. Strategic Advisor will not be eligible for any employee benefits. Taxes will be the sole responsibility of Strategic Advisor.

4. Additional Activities

(a) Strategic Advisor agrees that during the Strategic Advisory Period and for one year thereafter, Strategic Advisor will not attempt to induce any employee or employees of Ionis to terminate their employment with, or otherwise cease their relationship with Ionis.

(b) Strategic Advisor acknowledges that Ionis has developed, through an extensive acquisition process, valuable information regarding actual or prospective partners, licensors, licensees, clients, customers and accounts of Ionis ("***Trade Secret Information***"). Strategic Advisor acknowledges that Strategic Advisor's use of such Trade Secret Information after the termination of the Strategic Advisory Period would cause Ionis irreparable harm. Therefore, Strategic Advisor also agrees that Strategic Advisor will not utilize any Trade Secret Information to solicit the business relationship or patronage of any of the actual or prospective partners, licensors, licensees, clients, customers or accounts of Ionis.

(c) The restrictions set forth in this Section 4 are considered by the parties to be reasonable for the purposes of protecting Ionis' business. However, if any such restriction is found by a court of competent jurisdiction to be unenforceable because it extends for too long a period of time or over too great a range of activities or in too broad a geographic area, it will be interpreted to extend only over the maximum period of time, range of activities or geographic areas as to which it may be enforceable.

5. Confidential Information

(a) Ionis possesses confidential information that has been created, discovered, developed by, or otherwise become known to Ionis (including, without limitation, information created, discovered, developed or made known by Strategic Advisor arising from the Strategic Advisory Services).

(i) All such information is hereinafter referred to as "***Confidential Information***." By way of illustration, but not limitation, Confidential Information includes: (A) inventions, developments, designs, improvements, trade secrets, ideas, formulas, source and object codes, programs, other works of authorship, organisms, plasmids, expression vectors, know-how, processes, cell lines, discoveries, techniques, data and documentation systems (hereinafter collectively referred to as "***Inventions***"); and (B) information regarding plans for research, development, new products, clinical data, pre-clinical product data, clinical trial patient data, marketing and selling, business plans, budgets and unpublished financial statements, licenses, prices and costs, as well as information regarding the skills and compensation of employees of Ionis.

(ii) All Confidential Information will be the sole property of Ionis and its assigns, and Ionis and its assigns will be the sole owner of all patents, copyrights and other rights in connection with such Confidential Information. At all times, both during the term of this Agreement and for five years after its termination, Strategic Advisor will keep in confidence and trust all Confidential Information and will not use, disclose, lecture upon or publish any Confidential Information or anything related to such information without Ionis' prior written consent. Any permitted disclosures will be made in strict compliance with the Ionis publication and presentation clearance policy.

(b) Strategic Advisor also understands that Ionis has received and in the future, will receive valuable information from third parties that is confidential or proprietary ("***Third-Party Information***") subject to a duty on the part of Ionis to maintain the confidentiality of such information and to use it only for certain limited purposes. During the term of this Agreement and for five years thereafter, Strategic Advisor will hold Third-Party Information in the strictest confidence and will not disclose or use Third-Party Information except as permitted by the agreement between Ionis and such third party, unless expressly authorized to act otherwise by an officer of Ionis in writing. Any permitted disclosures will be made in strict compliance with Ionis publication and presentation clearance policy.

(c) The obligations of Section 5 will not apply to information that Strategic Advisor can establish by written records: (i) was known by Strategic Advisor prior to the receipt of Confidential Information; (ii) was disclosed to Strategic Advisor by a third party having the right to do so; (iii) was, or subsequently became, in the public domain through no fault of Strategic Advisor, its officers, directors, affiliates employees or agents; (iv) was independently developed by Strategic Advisor without use of Confidential Information; or (v) was disclosed by Strategic Advisor pursuant to any judicial, governmental or stock exchange request, requirement or order, so long as Strategic Advisor provided Ionis with sufficient prior notice in order to allow Ionis to contest such request, requirement or order.

6. Inventions

In the course of performing Strategic Advisory Services for Ionis, Strategic Advisor may develop new ideas or Inventions or make other contributions of value to Ionis.

(a) Strategic Advisor hereby assigns to Ionis Strategic Advisor's entire right, title and interest in and to any and all Inventions (and all patent rights, copyrights, and all other rights in connection therewith, hereinafter referred to as "***Proprietary Rights***") whether or not patentable or registrable under patent, copyright or similar statutes, made or conceived of or reduced to practice or learned by Strategic Advisor, either alone or jointly with others, as a result of performing Strategic Advisory Services hereunder. All Inventions assigned to Ionis pursuant to this section will be known as "***Company Inventions***". Strategic Advisor agrees that all Proprietary Rights and Company Inventions are Ionis' sole property. Strategic Advisor agrees, upon request, to execute, verify and deliver assignments of such Proprietary Rights to Ionis or its designee. Strategic Advisor understands that, to the extent this Agreement will be construed in accordance with the laws of any state which precludes a requirement in an agreement to assign certain classes of inventions made by an individual acting as a Strategic Advisor, this section will be interpreted not to apply to any inventions that a court rules and/or Ionis agrees falls within such classes.

(b) Strategic Advisor further agrees to assist Ionis in every proper way to obtain, from time to time, and to enforce United States and foreign Proprietary Rights relating to Company Inventions in any and all countries. To that end Strategic Advisor will execute, verify and deliver such documents and perform such other acts (including appearances as a witness) as Ionis may reasonably request for use in applying for, obtaining, sustaining and enforcing such Proprietary Rights relating to Company Inventions. Strategic Advisor's obligation to assist Ionis in obtaining and enforcing Proprietary Rights relating to Company Inventions in any and all countries will continue beyond the termination of this Agreement, but Ionis will compensate Strategic Advisor at a reasonable rate after such termination for the time actually spent by Strategic Advisor at Ionis' request in connection with such assistance. If Ionis is unable, after reasonable effort, to secure Strategic Advisor's signature on any document needed to apply for or prosecute any Proprietary Rights relating to a Company Invention, Strategic Advisor hereby irrevocably designates and appoints Ionis and its duly authorized officers and agents as her agent and attorney in fact, to act for and on Strategic Advisor's behalf to execute, verify and file any such applications and to do all other lawfully permitted acts to further the prosecution and issuance of any such Proprietary Rights with the same legal force and effect as if executed by Strategic Advisor.

(c) During the term of this Agreement, Strategic Advisor will promptly disclose to Ionis, or any persons designated by it, fully and in writing and will hold in trust for the sole right and benefit of Ionis any and all Company Inventions, whether or not patentable or protectable by copyright. At the time of each such disclosure, Strategic Advisor will advise Ionis in writing of any Inventions that Strategic Advisor believes are not subject to the assignment provisions of Section 6(a) above, and Strategic Advisor will at that time provide to Ionis in writing all evidence necessary to substantiate that belief. Strategic Advisor will not be obligated to disclose information received by Strategic Advisor from others under a contract of confidentiality. In addition, after termination of this Agreement, Strategic Advisor will disclose to Ionis all patent applications filed by Strategic Advisor relating to any Company Inventions or relating to any work performed by Strategic Advisor on behalf of Ionis.

7. Previous Strategic Advisory Relationships

Strategic Advisor represents that Strategic Advisor's performance of Strategic Advisory Services, as well as Strategic Advisor's performance of the rest of Strategic Advisor's obligations under the terms of this Agreement, will not breach any agreement to keep in confidence any proprietary information acquired by Strategic Advisor in confidence or in trust from another entity prior to the date of this Agreement. Strategic Advisor agrees not to bring to Ionis or to use in the performance of Strategic Advisory Services for Ionis any materials or documents of a present or former employer or client of Strategic Advisor, or any materials or documents obtained by Strategic Advisor under a confidentiality agreement imposed by reason of another of Strategic Advisor's Strategic Advisory relationships, unless such materials or documents are generally available to the public or Strategic Advisor has authorization from such present or former employer or client for the possession and unrestricted use of such materials.

8. Termination; Survival

(a) The term of this Agreement will begin on January 15, 2018 and will end when terminated by either Ionis or Strategic Advisor. Ionis may terminate this Agreement at any time for any reason by providing Strategic Advisor at least 90 days advance written notice. Strategic Advisor may terminate this Agreement at any time for any reason by providing Ionis at least 90 days advance written notice; *provided*, once Strategic Advisor delivers such a termination notice, Ionis may elect to accelerate the effective date of such termination. Upon any termination, Ionis will pay Strategic Advisor for any Strategic Advisory Services appropriately rendered and for any out of pocket expenses reasonably incurred on behalf of Ionis, up to and including the termination date.

(b) Sections 2(b)(ii) and 2(b)(iii), 9 and 10, will survive termination of this Agreement. In addition, upon expiration or termination of this Agreement, each party will be released from all obligations and liabilities to the other occurring or arising after the date of such expiration or termination, except that any termination or expiration of this Agreement will not relieve Strategic Advisor of Strategic Advisor's obligations under Sections 4, 5, 6, 7, 9, 10 and 11 hereof, nor will any such expiration or termination relieve Strategic Advisor or Ionis from any liability arising from any breach of this Agreement. Upon expiration or termination of this Agreement for any reason whatsoever, Strategic Advisor will promptly surrender and deliver to Ionis any and all notes, business records, memoranda, specifications, devices, formulas, molecules, cells, storage media, including calculations, sequences, data and other materials of any nature pertaining to Strategic Advisory Services for Ionis, as well as any documents or data of any description (or any reproduction of any documents or data) containing or pertaining to any Trade Secret Information, Ionis' Confidential Information or Third Party Information.

9. Arbitration

(a) Ionis and Strategic Advisor agree to resolve by arbitration all disputes, claims or controversies ("***Claims***"), past, present or future, whether or not arising out of this Agreement or its termination, that Ionis may have against Strategic Advisor or that Strategic Advisor may have against any of the following (i) Ionis; (ii) Ionis officers, directors; employees or agents; (iii) Ionis' subsidiary or affiliated entities, joint ventures, or joint employers; (iv) Ionis' benefit plans or the plans' sponsors, fiduciaries, administrators, affiliates and agents; and/or (v) all successors and assigns of any of the foregoing. The Claims covered by this Agreement include all disputes that Ionis or Strategic Advisor could otherwise pursue in state or federal court including, but not limited to, Claims based on any state, federal, or local statute, regulation or ordinance (including Claims for discrimination, retaliation, harassment, unpaid wages or violation of state or federal wage and hour laws), as well as common law Claims (including Claims for breach of contract, breach of the implied covenant of good faith and fair dealing, wrongful discharge, defamation, misrepresentation, fraud, or infliction of emotional distress). Ionis and Strategic Advisor anticipates that this Section 9 provides the benefits of a speedy, less formal, impartial, final and binding dispute resolution procedure.

(b) To the maximum extent permitted by law, Strategic Advisor hereby waives any right to bring on behalf of persons other than Strategic Advisor, or to otherwise participate with other persons in, any class, collective or representative action (i.e. a type of lawsuit in which one or several persons sue on behalf of a larger group of persons).

(c) The arbitration will be conducted by a single neutral arbitrator in accordance with the then- current Commercial Arbitration and Mediation Procedures of the American Arbitration Association ("***AAA***"). The arbitration will take place in San Diego, California. Ionis will pay the arbitrator's fee and will bear all administrative charges by AAA. All parties will be entitled to engage in reasonable pre-hearing discovery to obtain information to prosecute or defend the asserted claims. Any disputes between the parties regarding the nature or scope of discovery will be decided by the arbitrator. The arbitrator will hear and issue a written ruling upon any dispositive motions brought by either party, including but not limited to, motions for summary judgment or summary adjudication of issues. After the hearing, the arbitrator will issue a written decision setting forth the award, if any, and explaining the basis therefore. The arbitrator will have the power to award any type of relief that would be available in court. The arbitrator's award will be final and binding upon the parties and may be entered as a judgment in any court of competent jurisdiction. If there is conflict in the arbitration procedures set forth in this Agreement and the AAA rules specified above, the AAA rules will control. Notwithstanding the foregoing, and regardless of what is provided by the AAA rules, the arbitrator will not have authority or jurisdiction to consolidate claims of different individuals or entities into one proceeding, nor will the arbitrator have authority or jurisdiction to hear the arbitration as a class action. As noted above, Strategic Advisor has agreed to waive any right to bring any class, collective or representative action. To the extent that the class, collective or representative action waiver described above is not enforceable, the issue of whether to certify any alleged or putative class for a class action proceeding must be decided by a court of competent jurisdiction. The arbitrator will not have authority or jurisdiction to decide class certification, collective or representative action issues. Until any class certification, collective, or representative action issues are decided by the court, all arbitration proceedings will be stayed, and the arbitrator will take no action with respect to the matter. However, once any issues regarding class certification, collective, or representative action have been decided by the court, the arbitrator will have authority to decide the substantive claims.

10. Indemnification

(a) Ionis will indemnify, defend and hold Strategic Advisor harmless against any and all losses, costs, expenses and damages (including reasonable attorney's fees) ("Loss(es)") incurred as a result of any third party claims, suits, actions, demands or proceedings resulting or arising from the performance of Strategic Advisory Services as specifically directed by Ionis in accordance with the Agreement to the extent such Loss(es) are not the result of Strategic Advisor's gross negligence, intentional misconduct or material breach of this Agreement.

(b) Ionis' agreement to indemnify, defend and hold Strategic Advisor harmless is conditioned upon the Strategic Advisor (i) providing written notice to Ionis of any claim, demand or action arising out of the indemnified activities within thirty (30) days after Strategic Advisor has knowledge of such claim, demand or action, *provided* that the failure to so notify Ionis shall not relieve Ionis of its obligations hereunder except to the extent such failure shall have actually materially prejudiced Ionis; (ii) permitting Ionis to assume full responsibility to investigate, prepare for and defend against any such claim or demand; (iii) assisting Ionis, at Ionis' reasonable expense, in the investigation of, preparation of and defense of any such claim or demand; (iv) undertaking reasonable steps to mitigate any loss, damage or expense with respect to the applicable claim or demand; and (v) not settling such claim or demand without Ionis' prior written consent.

(c) Ionis will endeavor to include Strategic Advisor as a covered attorney on its insurance policy for attorneys who advise Ionis.

11. Miscellaneous

(a) The rights and liabilities of the parties hereto will bind and inure to the benefit of their respective successors, heirs, executors and administrators, as the case may be; *provided that*, as Ionis has specifically contracted for Strategic Advisor's services, Strategic Advisor may not assign or delegate Strategic Advisor's obligations under this Agreement either in whole or in part without Ionis' prior written consent.

(b) Because Strategic Advisor's services are personal and unique and because Strategic Advisor has access to and become acquainted with Ionis' Confidential Information, the parties agree that in the event of a threatened or actual material breach of this Agreement by Strategic Advisor injunctive relief would be appropriate. As such, Ionis has the right to enforce this Agreement and any of its provisions by injunction, specific performance or other equitable relief without prejudice to any other rights and remedies that Ionis may have for a breach of this Agreement.

(c) This Agreement will be governed by and construed according to the laws of the State of California as such laws are applied to contracts entered into and performed entirely within such State. If any provision of this Agreement is held to be or becomes invalid, illegal or unenforceable, such provision will be validly reformed to approximate as nearly as possible the intent of the parties and the remainder of this Agreement will not be affected thereby and will remain valid and enforceable to the greatest extent permitted by law.

(d) This Agreement, and all other documents mentioned herein, constitute the final, exclusive and complete understanding and agreement of the parties hereto and supersedes all prior understandings and agreements. Any waiver, modification or amendment of any provision of this Agreement will be effective only if in writing and signed by the parties hereto.

(e) Any notices required or permitted hereunder will be given to the appropriate party at the address specified on the Summary Page or at such other address as the party will specify in writing. Such notice will be deemed given upon personal delivery to the appropriate address, or by facsimile transmission (receipt verified and with confirmation copy followed by another permitted method), sent by express courier service, or, if sent by certified or registered mail, three (3) days after the date of mailing.

Exhibit 10.83

CONFIDENTIAL **Execution Version**

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

AMENDMENT NO. 1 TO COLLABORATION AND LICENSE AGREEMENT

This Amendment No. 1 to Collaboration and License Agreement ("**First Amendment**") is made and entered into effective as of December 17, 2021 ("**First Amendment Effective Date**") by and between **BicycleTx Limited**, a company incorporated in England and Wales with a place of business at Building 900, Babraham Research Campus, Cambridge CB22 3AT, UK ("**BicycleTx**"), and Ionis Pharmaceuticals, Inc., a Delaware corporation with a principal place of business at 2855 Gazelle Court, Carlsbad, California 92010, USA ("**Ionis**"). BicycleTx and Ionis are referred to herein individually as a "**Party**" and collectively as the "**Parties**".

BACKGROUND

WHEREAS, BicycleTx and Ionis entered into that certain Collaboration and License Agreement dated as of July 9, 2021 (the "**Agreement**"), pursuant to which the Parties agreed to collaborate in the research and development of products incorporating TfR1 Bicycles directed against certain Targets;

WHEREAS, the Agreement provides for BicycleTx to perform the Research Activities, subject to certain terms and conditions, including **[***]** at BicycleTx's cost, with additional BicycleTx work requested by Ionis over and above such **[***]** annually to be discussed in good faith and mutually agreed by the Parties;

WHEREAS, the Parties now seek to conduct certain additional activities to evaluate the potential for TfR1 Bicycles **[***]**, and the Parties thus desire to amend the Agreement to provide for BicycleTx to perform such additional activities at Ionis' cost, as further set forth in this First Amendment; and

WHEREAS, Section 12.3 of the Agreement provides that the Agreement may only be modified by a written instrument duly executed by authorized representatives of each Party.

NOW, THEREFORE, the Parties desire, for good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, to amend the Agreement as set forth in this First Amendment.

ARTICLE 1
DEFINITIONS

1.1 **Capitalized Terms.** Capitalized terms used in this First Amendment shall have the meanings set forth in the Agreement, unless otherwise defined in in this First Amendment. Section references set forth in this First Amendment shall refer to section references in this First Amendment, unless expressly stated to refer to sections of the Agreement.

ARTICLE 2
AMENDMENT

2.1 **Additional Activities**. BicycleTx will perform the research activities set forth on Schedule 1 attached hereto (the "**Additional Activities**") during the period beginning on [***] and continuing until the first anniversary of such date (the "**Additional Research Period**") in accordance with Section 4.5.1(a) of the Agreement. The Additional Activities shall be deemed Research Activities under the Agreement, pursuant to Section 4.2.2 thereof, subject to the terms and conditions of this First Amendment. Ionis shall use Commercially Reasonable Efforts to perform the Additional Activities allocated to it at its sole cost and expense.

2.2 **Amendment of the Research Plan**. The Research Plan shall be deemed amended pursuant to Section 4.2.3 of the Agreement as of the First Amendment Effective Date to incorporate the Additional Activities, without the requirement for a separate written agreement by the JSC.

2.3 **Level of Effort; Payment**. BicycleTx shall allocate [***]. Within [***] Business Days after the First Amendment Effective Date, Ionis shall pay to BicycleTx the sum of $1,560,000, of which $780,000 is in consideration of the signing of this First Amendment, and the remaining $780,000 is in consideration of the performance by BicycleTx of the Additional Activities for the duration of the Additional Research Period (such total amount, the "**Additional Activities Fee**").

2.4 **Initial Period**.

2.4.1 **Determination of Success Criteria and Initial Data Package**. During the first six-month period of the Additional Research Period (the "**Initial Period**"), the Parties, through the JSC, shall discuss in good faith and mutually agree upon (a) the success criteria by which the Parties will determine whether the initial goals of the Additional Activities have been achieved, and whether the Parties should continue to perform such Additional Activities for the remainder of the Additional Research Period (the "**Success Criteria**") and (b) the nature and scope of the data generated by BicycleTx in the course of performing the Additional Activities during the Initial Period, which data BicycleTx will deliver to the JSC pursuant to Section 2.4.2 (the "**Initial Data Package**").

2.4.2 **Data Sharing**. No later than the date that is [***] prior to the expiration of the Initial Period, BicycleTx shall deliver to the JSC the Initial Data Package. The Parties shall review and discuss the Initial Data Package and, prior to the expiration of the Initial Period, shall mutually determine in good faith whether the Success Criteria have been achieved.

2.4.3 **Decisions by Consensus**. The Parties' agreement upon the Success Criteria pursuant to Section 2.4.1 and determination of whether the Success Criteria have been achieved pursuant to Section 2.4.2 shall not be subject to the final decision-making authority of either Party and shall be made by the Parties by consensus only. If the Parties are unable to agree upon the Success Criteria or their achievement, then Section 2.5.2 shall apply.

2.5 **Follow-On Period; Termination of Additional Activities**.

2.5.1 **Follow-On Period**. If the Parties mutually agree upon the Success Criteria and mutually determine that the Success Criteria have been achieved, then BicycleTx shall continue to perform the Additional Activities for the remainder of the Additional Research Period (the "**Follow-On Period**"), and BicycleTx shall be entitled to retain the entire Additional Activities Fee. The Parties, through the JSC, shall discuss in good faith and mutually agree upon the nature and scope of the data generated by BicycleTx in the course of performing the Additional Activities during the Follow-On Period, which data BicycleTx will deliver to the JSC pursuant to this Section 2.5.1 (the "**Follow-On Data Package**"). Promptly following the expiration of the Follow-On Period, BicycleTx shall deliver to the JSC the Follow-On Data Package. Upon expiration of the Follow-On Period, BicycleTx shall have no further obligation to perform any Additional Activities, unless the Parties mutually agree upon an extension to the Additional Research Period and the [***].

2.5.2 **Termination of Additional Activities**. If (a) the Parties cannot agree upon (i) the Success Criteria prior to the end of the Initial Period, or (ii) whether the Success Criteria have been achieved prior to the end of the Initial Period, or (b) the Parties agree upon the Success Criteria but do not agree that the Success Criteria have been achieved by the end of the Initial Period, then in each case ((a) and (b)), BicycleTx (A) shall have no further obligation to perform any Additional Activities, (B) shall be entitled to retain $780,000 of the Additional Activities Fee as consideration for signing of this First Amendment, (C) shall refund to Ionis the remaining $780,000 of the Additional Activities Fee, and (D) the Additional Research Period shall be deemed terminated upon the expiration of the Initial Period.

ARTICLE 3
MISCELLANEOUS

3.1 **No Waiver**. Nothing in this First Amendment is intended to operate as a waiver of any claims either Party may have against the other Party arising prior to the date of this First Amendment under the Agreement. Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver shall be effective unless it is in writing and signed by the Party waiving such term or condition. The waiver by either Party hereto of any right hereunder or of a breach by the other Party shall not be deemed a waiver of any other right hereunder or of any other breach by such other Party whether of a similar nature or otherwise.

3.2 **Miscellaneous.** This First Amendment and the performance, enforcement, breach, and termination hereof shall be interpreted, governed by, and construed in accordance with the laws of the State of New York, United States excluding any conflicts or choice of law rule or principle that might otherwise refer construction or interpretation of this First Amendment to the substantive law of another jurisdiction. Any dispute arising from or relating to this First Amendment will be subject to resolution in accordance with Section 12.2 of the Agreement. Except as specifically amended by this First Amendment, the terms and conditions of the Agreement shall remain in full force and effect. Except to the extent expressly provided herein, the Agreement, as amended by this First Amendment, including all appendices, exhibits and schedules to each of the foregoing, sets forth the entire agreement and understanding between the Parties with respect to the subject matter of the Agreement (as amended) and all prior agreements, understandings, promises, and representations, whether written or oral, with respect thereto are superseded hereby. This First Amendment may be executed in two or more counterparts in original, facsimile, PDF, or other electronic format, each of which shall be an original, and all of which together shall constitute one instrument.

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THIS AMENDMENT NO. 1 TO COLLABORATION AND LICENSE AGREEMENT is executed by the authorized representatives of the Parties as of the First Amendment Effective Date.

BICYCLETX LIMITED

By: /s/Michael Skynner

Name: Michael Skynner

Title: COO

IONIS PHARMACEUTICALS, INC.

By: /s/Brett Monia

Name: Brett Monia

Title: CEO

Schedule 1
Additional Activities

[***]

Exhibit 10.84

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

COLLABORATION AND LICENSE AGREEMENT

by and between

Akcea Therapeutics, Inc.

and

AstraZeneca AB

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SCHEDULES

This COLLABORATION AND LICENSE AGREEMENT (the "***Agreement***") is executed as of December 6, 2021 (the "***Execution Date***"), by and between **AstraZeneca AB**, a company incorporated in Sweden under no. 556011-7482 with its registered office at SE-151 85 Södertälje, Sweden and with offices at SE-431 83 Mölndal, Sweden ("***AstraZeneca***"), **Akcea Therapeutics, Inc.**, a Delaware corporation, having its principal place of business at 22 Boston Wharf Road, Boston, MA 02210 ("***Akcea***") and with respect to Article 14 and Section 17.10 only, Ionis Pharmaceuticals, Inc., a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad, CA 92010 ("***Ionis***"). AstraZeneca and Akcea will be referred to herein individually as a "***Party***" and collectively as the "***Parties***".

RECITALS

WHEREAS, AstraZeneca and Akcea are biopharmaceutical companies focused on developing, manufacturing and commercializing therapeutics on a global basis;

WHEREAS, pursuant to that certain Development, Commercialization and License Agreement between Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc. dated March 14, 2018 (the "***Ionis/Akcea Agreement***"), Akcea has an exclusive license from its Affiliate, Ionis, to develop, manufacture and commercialize the Licensed Compound (as defined below) to treat all types of TTR amyloidosis (ATTR), a systemic, progressive and fatal disease;

WHEREAS, the Licensed Compound is currently being investigated in Phase 3 Clinical Trials, and the Parties desire to further Develop and Commercialize the Licensed Compound;

WHEREAS, AstraZeneca is granted certain rights under this Agreement, including an exclusive license to Develop and Commercialize Licensed Products (as defined below) in the Territory.

NOW, THEREFORE, in consideration of the premises and mutual covenants herein contained, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

ARTICLE 1
OVERVIEW

1.1 **Development and Commercialization**. The Parties intend that under this Agreement: (a) the Parties will jointly Develop the Licensed Product pursuant to a Development Plan and Budget and the Parties will share the costs of such Development activities according to certain cost-sharing ratios (and as further described in Section 2.4); (b) the Parties will jointly Commercialize, and perform Medical Affairs activities with respect to, the Licensed Product in the United States pursuant to a U.S. Commercialization Plan and Budget and U.S. Medical Affairs Plan and Budget, as applicable, unless and until Akcea opts out of such activities in accordance with Section 3.6, and the Parties will share the costs of such activities according to certain cost-sharing ratios (as further described in Section 3.4); and (c) AstraZeneca will have the sole right to Commercialize the Licensed Product in all other countries of the Territory pursuant to a corresponding ROW Commercialization Plan.

1.2 **Governance**. The Parties have agreed to form (a) a joint steering committee to oversee and coordinate the Development, Manufacturing, Commercialization and other Exploitation activities with respect to the Licensed Product under this Agreement, (b) a joint development committee reporting to the JSC to oversee the Development of the Licensed Product under this Agreement, (c) a joint commercialization and medical committee reporting to the JSC to oversee the Parties' Commercialization and Medical Affairs activities for the Licensed Product under this Agreement, and (d) a regulatory working group reporting to the JDC to develop a Regulatory Strategy and coordinate the preparation and submission of Regulatory Filings in the Territory. The JSC, JDC, JCMC and RWG's core focus will be the Exploitation of Licensed Products for the U.S. and will serve as information-sharing bodies with respect to Exploitation of the Licensed Products for the ROW Territory.

1.3 **Purpose**. The purpose of this Article 1 is to provide a high-level overview of the roles, responsibilities, rights and obligations of each Party under this Agreement, and therefore, this Article 1 is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

ARTICLE 2
DEVELOPMENT

2.1 **Development Diligence**. From the Closing Date, subject to and in accordance with the terms and conditions of this Agreement, (a) Akcea will use Commercially Reasonable Efforts to perform its activities under the Development Plan and Budget and (b) AstraZeneca will use Commercially Reasonable Efforts to (i) obtain Regulatory Approval for a Licensed Product in [***] and (ii) on a [***] basis, to obtain Regulatory Approval for a Licensed Product in such [***], in each case ((i) and (ii)), in accordance with the Development Plan and Budget.

2.2 **Development Plan and Budget and Updates**.

2.2.1 **Development Plan and Budget**. Prior to the Execution Date, the Parties have agreed upon an initial development plan and corresponding budget for the Licensed Product, which initial development plan and budget is attached hereto as Schedule 2.2.1 (such development plan and budget, as it may be modified in accordance with the terms and conditions of this Agreement, the "***Development Plan and Budget***"). The initial Development Plan and Budget includes (and, subject to Section 3.6.2(a)(i), will at all times include): (a) prior to [***] in each of the Initial Indications, the Regulatory Strategy, (b) the high-level Development activities that are to be undertaken by the Parties to obtain Regulatory Approval for the Licensed Product in each Major Market for each Initial Indication, including the Development activities that are to be undertaken by the Parties for the Clinical Trials that are ongoing as of the Execution Date, (c) the allocation of responsibilities between the Parties (which allocation will be consistent with Section 2.2.2) for all activities under the Development Plan and Budget, (d) the estimated timelines for all activities under the Development Plan and Budget and (e) a detailed written budget for the performance of the U.S. Development Activities and Global Development Activities under the Development Plan and Budget for the [***] subsequent Calendar Years, the [***] of which will be (on a rolling [***] basis) a reasonably detailed budget with costs categorized based on whether the activities are U.S. Development Activities, Global Development Activities or ROW Development Activities, and the next [***] of which will be a high-level estimated budget. The terms of, and activities set forth in, the Development Plan and Budget will at all times be designed to be in compliance with all applicable Laws and to be conducted in accordance with professional and ethical standards customary in the pharmaceutical industry, and, where applicable, each Party's respective health care compliance policies and applicable standard operating procedures.

2.2.2 Allocation of Development Activities. The Development Plan and Budget will include the allocation of responsibilities for all Development activities for the Licensed Product. On an activity-by-activity basis, the Party with primary responsibility for a particular Development activity will be the "***Lead Development Party***" for such Development activity. Subject to Section 4.2.1(a) and Section 4.2.1(b), unless otherwise mutually agreed by the Parties and set forth in the Development Plan and Budget, the Development Plan and Budget will provide that: (a) Akcea will be the Lead Development Party for all Clinical Trials ongoing as of the Execution Date and (b) AstraZeneca will be the Lead Development Party for (i) all Clinical Trials initiated after the Closing Date and (ii) all Development activities that are [***] to support obtaining and maintaining Regulatory Approval or label expansion of a Licensed Product in the ROW Territory (such clause (b)(ii) Development activities, "***ROW Development Activities***").

2.2.3 Changes to the Development Plan and Budget. If a Party wishes to make a change to the Development Plan and Budget, then such Party will submit its proposed change to the JDC for the JDC to review and discuss. Except for any change proposed by [***] and, subject to Section 3.6.2(a)(i), the JDC will revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve such proposed change. The JSC shall review and determine whether to approve any such proposed change to the Development Plan and Budget. Each such update to the Development Plan and Budget will become effective and will supersede the previous Development Plan and Budget upon approval thereof by the JSC (which approval will be memorialized in the minutes of such JSC meeting). For clarity, any update or amendment to the Development Plan and Budget proposed by AstraZeneca with respect to [***].

2.3 Development Activities Prior to Closing Date. After the Execution Date and prior to the Closing Date, Akcea will continue performing Development activities for the Licensed Product in a manner, and with the level of resources, consistent with Akcea's Development activities prior to the Execution Date. Akcea will promptly notify AstraZeneca if Akcea is required to make any material changes to such performance (a) to comply with any changes in applicable Law, (b) to comply with specific requirements imposed by Regulatory Authorities, or (c) as Akcea reasonably determines in good faith are [***], and, following such notice, Akcea will be permitted to make such changes to such performance.

2.4 Development Costs.

2.4.1 Shared Development Costs. The Parties will share, in accordance with Section 2.4.1(a) and subject to the reconciliations set forth in Section 2.4.1(b), the Eligible Development Expenses that are reasonably allocable to Development of the Licensed Product prior to the Opt-Out Date, if any, that (x) are [***] to support obtaining and maintaining Regulatory Approval or label expansion for the Licensed Product in the U.S. (such Development activities, "***U.S. Development Activities***") or (y) are not ROW Development Activities or U.S. Development Activities (such Development activities, "***Global Development Activities***").

(a) **Share Ratios**.

(i) Subject to Section 2.4.1(b)(ii), Akcea will bear [***]% and AstraZeneca will bear [***]% of all Eligible Development Expenses incurred in conducting the U.S. Development Activities or Global Development Activities from and after the Closing Date through December 31, 2025.

(ii) Subject to Section 2.4.1(b)(ii) and Section 2.4.1(b)(iii), Akcea will bear [***]% and AstraZeneca will bear [***]% of all Eligible Development Expenses incurred in conducting the U.S. Development Activities from and after January 1, 2026, and Akcea will bear [***]% and AstraZeneca will bear [***]% of all Eligible Development Expenses incurred in conducting the Global Development Activities from and after January 1, 2026.

(b) **Shared Development Cost Payment Reconciliation**. Unless and until the Opt-Out Date occurs (and for the Calendar Quarter in which the Opt-Out Date occurs), the following provisions shall apply:

(i) No later than [***] after the end of each Calendar Quarter, each Party will deliver to the other Party a non-binding estimate that sets forth the Eligible Development Expenses incurred by or on behalf of such Party in connection with the performance of the U.S. Development Activities and Global Development Activities during such Calendar Quarter. No later than [***] after the end of each Calendar Quarter, each Party will deliver to the other Party a written report that sets forth in detail the actual Eligible Development Expenses incurred by or on behalf of such Party in connection with the performance of U.S. Development Activities and Global Development Activities during such Calendar Quarter, including a comparison of its Eligible Development Expenses for a Development activity to the amount budgeted in the Development Plan and Budget for such activity (such report of actual expenses, the "***Development Cost Share Notice***"). Each Party will provide the other Party with supporting documentation of such Eligible Development Expenses if reasonably requested by the other Party. For each Calendar Quarter, no later than [***] after receipt of the Development Cost Share Notice for such Calendar Quarter from each Party, the Party that incurred less than its allocation of Eligible Development Expenses during such Calendar Quarter will make a balancing payment to the other Party to effect the cost-sharing ratios set forth in Section 2.4.1(a), to the extent the amounts set forth in the Development Cost Share Notices are undisputed. Any dispute regarding amounts set forth in a Development Cost Share Notice will be promptly referred to the JSC for resolution, and if the JSC determines that any disputed amount should be included in the applicable Development Cost Share Notice, then the Party that incurred less than its allocation of Eligible Development Expenses during such Calendar Quarter (taking into account any balancing payments previously made for such Calendar Quarter pursuant to the immediately preceding sentence) will make a balancing payment to the other Party to effect the cost-sharing ratios set forth in Section 2.4.1(a) within [***] of the JSC determination.

(ii) If any ROW Development Activities conducted from and after the Closing Date relate to a Clinical Trial that [***] and (1) AstraZeneca will deliver to Akcea [***], and (2) AstraZeneca will [***] in Section 2.4.1(a) for Global Development Activities, to the extent the [***] Section 11.5.1 or Section 11.6.1; *provided* that in no event will [***]; *provided, further,* that any dispute regarding [***] will be promptly referred to the JSC for resolution, and if the JSC determines that [***], AstraZeneca will [***] Section 11.5.1 or Section 11.6.1. Any [***]. As soon as reasonably practicable, AstraZeneca will promptly notify Akcea if it [***] and provide [***].

(iii) If any U.S. Development Activities conducted from and after [***] relate to a Clinical Trial that [***], then such activities will be [***] and (1) Akcea will have the right to [***] and (2) Akcea will [***]; *provided* that in no event will [***]. Any [***]; *provided* that [***], then AstraZeneca [***].

(iv) Notwithstanding the foregoing, the [***] from a Clinical Trial (A) in any annual or periodic safety reports to any Regulatory Authority with respect to the Licensed Product or (B) in the safety information portion of the Licensed Product labeling without the Licensed Product being approved for the applicable indication that was the subject of such Clinical Trial, in either case ((A) or (B)), shall not alone result in [***] under Section 2.4.1(b)(ii) or Section 2.4.1(b)(iii).

2.4.2 ROW Eligible Development Expenses. Except as set forth in Section 2.4.1(b)(ii), [***] will be responsible for [***] costs and expenses incurred in connection with the ROW Development Activities for the Licensed Product.

2.5 Additional Development.

2.5.1 Additional Development. If AstraZeneca proposes to conduct any Development activity that would constitute U.S. Development Activities or Global Development Activities that is not set forth in the then-current Development Plan and Budget ("***Additional Development***"), then AstraZeneca will present to the JDC, to review, discuss and make a recommendation to the JSC as to whether to approve, a proposal to add such Additional Development to the Development Plan and Budget, including the countries in which such activities would be conducted, the allocation of performance of such activities between the Parties, and, if applicable, a summary of the Regulatory Approval or expanded or modified label that AstraZeneca is seeking to obtain based on the data from such Additional Development (which summary will be consistent with any proposals prepared by AstraZeneca as part of its internal approval process for such Development) (an "***Additional Development Proposal***"). The JSC shall review and determine whether to approve any such Additional Development Proposal. Each Additional Development Proposal will describe in reasonable detail the Development activities that AstraZeneca desires to conduct, including a proposed timeline and budget and an analysis of the business opportunity and revenue potential for such Additional Development and, with respect to any Clinical Trial, an outline of the Clinical Trial, the proposed enrollment criteria, the number of patients to be included, the endpoints to be measured, and the statistical design and powering.

2.5.2 JSC Decision Regarding Additional Development.

(a) **JSC Approval**. If the JSC approves an Additional Development Proposal, then, upon such an approval: (i) the Additional Development set forth in such Additional Development Proposal will be deemed "U.S. Development Activities" or "Global Development Activities" (as applicable) for purposes of this Agreement and (ii) the JDC will update the Development Plan and Budget to include such activities.

(b) **No JSC Approval**. If the JSC fails to approve an Additional Development Proposal, then, upon such a failure, except as otherwise set forth in Section 2.5.3, the Additional Development proposed in the Additional Development Proposal will not be included in the Development Plan and Budget and AstraZeneca will have the right to conduct such Additional Development solely in accordance with Section 2.5.3.

2.5.3 Independent Performance of Additional Development. If the JSC fails to approve for inclusion in the Development Plan and Budget the Additional Development Proposal (or any modified version thereof), then AstraZeneca will have the right, upon written notice to Akcea, to conduct such Additional Development set forth in the Additional Development Proposal [***], subject to Section 2.5.4. AstraZeneca will conduct such Additional Development in accordance with the applicable Additional Development Proposal (including the budget therein) previously provided to the JSC that the JSC declined to approve; *provided* that, upon written notice to Akcea, AstraZeneca may update or amend such Additional Development Proposal (and budget therein) so long as AstraZeneca does not materially change the scope of Additional Development to be conducted without repeating the Additional Development Proposal process set forth in Section 2.5.1 and Section 2.5.2. No Development activities included in an Additional Development Proposal may be included in or contemplated by the Development Plan and Budget if not approved by the JSC; *provided* that any Additional Development Proposal that is not approved by the JSC may be described in the Development Plan and Budget for informational purposes only and will be marked as not approved by the JSC and not subject to the Parties' respective rights and obligations related to the Development Plan and Budget under this Agreement. AstraZeneca will keep the JSC reasonably informed of any progress and results of activities for such Additional Development undertaken by it or on its behalf at each regularly scheduled meeting thereof.

2.5.4 Successful Additional Development. With respect to any Additional Development conducted pursuant to Section 2.5.3, if the Additional Development [***], then AstraZeneca will have the right to deduct an amount equal to (a) [***] of Akcea's applicable share of the costs of such Additional Development with respect to such Additional Development activities conducted prior to [***] and (b) [***] of Akcea's applicable share of the costs of such Additional Development with respect to such Additional Development activities conducted on or after [***] (in each case which share will be based on whether such Additional Development was deemed to be U.S. Development Activities or Global Development Activities and the share ratios in Section 2.4.1(a)) from amounts payable to Akcea pursuant to Section 11.5.1 or Section 11.6.1; *provided* that in no event will the reductions under Section 2.4.1(b)(ii) and this Section 2.5.4 collectively reduce the amounts payable to Akcea pursuant to Section 11.5.1 or Section 11.6.1 (as adjusted by Section 11.6.2) by more than [***] in a given Calendar Quarter. Any excess amounts that would have otherwise been deducted in a Calendar Quarter shall be deducted from amounts payable to Akcea pursuant to Section 11.5.1 or Section 11.6.1 in successive Calendar Quarters until [***]; *provided* that if any such excess amounts remain undeducted after [***] successive Calendar Quarters (or, if earlier, the end of the Term), then [***]. Notwithstanding the foregoing, the [***] from an Additional Development activity (a) in any annual or periodic safety reports to any Regulatory Authority with respect to the Licensed Product or (b) in the safety information portion of the Licensed Product labeling without the Licensed Product being approved for the applicable indication that was the subject of such Additional Development, in either case ((a) or (b)), shall not alone result in any right for AstraZeneca to deduct costs pursuant to this Section 2.5.4.

2.5.5 Other Development. For the avoidance of doubt, neither Party will have the right to conduct any Development activities with respect to the Licensed Product that are not set forth in the Development Plan and Budget, except as expressly set forth in this Section 2.5. Notwithstanding anything to the contrary in this Agreement but without limiting each Party's rights and obligations under Article 8 and Article 9, the Parties agree that this Agreement may not be fit for the Development and Commercialization of [***], and neither Party shall clinically Develop or Commercialize [***] under this Agreement unless and until the Parties agree to appropriate amendments to this Agreement with respect thereto.

2.6 Records. Each Party will, and will cause its Affiliates and subcontractors to, maintain materially complete, current and accurate copies of records of all Development activities conducted by such Party pursuant to the Development Plan and Budget, and all results, data, developments and other Know-How made in conducting such activities. Such records will accurately reflect all such work done and results achieved in sufficient detail and in good scientific manner appropriate for applicable patent and regulatory purposes.

2.7 Disclosure of Results. Each Party will disclose to the other Party the results of all Development activities conducted by such Party under the Development Plan and Budget (other than [***]) in a reasonable manner as such results are obtained. Unless and until Akcea exercises the Opt-Out Right in accordance with Section 3.6, such disclosure will occur as soon as reasonably practicable. If Akcea exercises the Opt-Out Right in accordance with Section 3.6, then such disclosure will occur at each meeting of the JDC; *provided* that for any material results, such disclosure will occur as soon as reasonably practicable. The Parties will provide reports and analyses at each meeting of the JDC as contemplated under Section 6.3.3 (or as soon as practicable after the Completion of a Clinical Trial) detailing the current status of the Licensed Product under the Development Plan and Budget together with a summary of the data generated by such Party under the Development Plan and Budget.

ARTICLE 3
COMMERCIALIZATION AND MEDICAL AFFAIRS

3.1 Commercialization Generally.

3.1.1 Diligence. From the Closing Date, subject to and in accordance with the terms and conditions of this Agreement, (a) each Party will use Commercially Reasonable Efforts to perform its respective activities under the U.S. Commercialization Plan and Budget and the U.S. Medical Affairs Plan and Budget and (b) AstraZeneca will use Commercially Reasonable Efforts to (i) following receipt of Regulatory Approval for a Licensed Product [***], Commercialize such Licensed Product for the treatment of [***] and (ii) on a [***] basis, following receipt of Regulatory Approval for a Licensed Product in [***], Commercialize such Licensed Product [***] in such [***].

3.1.2 Responsibility. Except for the Co-Commercialization and Medical Affairs Activities to be performed by Akcea in the U.S. consistent with the U.S. Commercialization Plan and Budget and U.S. Medical Affairs Plan and Budget, AstraZeneca will have the sole right to Commercialize the Licensed Products in the Territory. As between the Parties, AstraZeneca and its Affiliates and its and their Sublicensees will have the sole right and will be solely responsible for (a) determining and establishing the pricing of Licensed Products and the terms of sale (including any rebates or discounts) in the Territory, (b) invoicing, booking and recording sales of Licensed Products in the Territory, (c) warehousing and distribution of Licensed Products in the Territory, and (d) handling all governmental rebates and similar payments that are due and owing with respect to Licensed Products in the Territory, including the submission of any required reports, including price reports, to any Governmental Authority. Moreover, as between the Parties, AstraZeneca and its Affiliates and its and their Sublicensees will have the sole right and will be solely responsible for handling all returns of commercialized Licensed Product, as well as all aspects of Licensed Product order processing, invoicing and collection, distribution, inventory and receivables, in the Territory. The Parties will perform Co-Commercialization and Medical Affairs Activities in accordance with [***] operating policies and processes to the extent (i) such policies and processes (and any updates or changes thereto) are [***] and (ii) [***].

3.2 U.S. Commercialization Plan and Budget, U.S. Medical Affairs Plan and Budget and Updates.

3.2.1 U.S. Commercialization Plan and Budget. Unless and until Akcea exercises the Opt-Out Right in accordance with Section 3.6, the Commercialization of the Licensed Product in the United States will be governed by a written plan that will include a corresponding budget (such Commercialization plan, as it may be modified in accordance with the terms and conditions of this Agreement, the "***U.S. Commercialization Plan and Budget***"). Only activities that are solely or primarily intended for the U.S. (including post approval commitments required by the FDA) will be classified as "U.S. Commercial" activities in the U.S. Commercialization Plan and Budget, and [***] will not exercise its final decision-making right in Section 6.6.5(e) to approve a U.S. Commercialization Plan and Budget that is inconsistent with the foregoing.

(a) **Interim U.S. Commercialization Plan and Budget**. Within [***] after the Closing Date (or longer time period as may be agreed by the Parties), AstraZeneca will prepare, in consultation and with input from Akcea, an interim U.S. Commercialization Plan and Budget to govern the Commercialization of the Licensed Product in the U.S. from the Closing Date through [***] (the "***Interim U.S. Commercialization Plan and Budget***"), which plan will contain (i) all Commercialization activities to be conducted by each Party for the Licensed Product in the United States from the Closing Date through [***], (ii) the allocation of responsibilities between the Parties (which allocation will be consistent with Schedule 3.2.1), (iii) the estimated timelines for all activities under the Interim U.S. Commercialization Plan and Budget, and (iv) a reasonably detailed written budget for the performance of all activities set forth in the Interim U.S. Commercialization Plan and Budget. AstraZeneca will present the Interim U.S. Commercialization Plan and Budget to the JCMC for the JCMC to review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve. The JSC shall review and determine whether to approve such Interim U.S. Commercialization Plan and Budget. The Interim U.S. Commercialization Plan and Budget will be considered the "U.S. Commercialization Plan and Budget" (including for purposes of cost-sharing) until a comprehensive U.S. Commercialization Plan and Budget is approved by the JSC pursuant to Section 3.2.1(b) (which approval will be memorialized in the minutes of such JSC meeting). The Interim U.S. Commercialization Plan and Budget will focus primarily on Commercialization of the Licensed Products for [***], and any Commercialization activities with respect to [***] will be included at a high level.

(b) **Comprehensive U.S. Commercialization Plan and Budget**. At such time as the JCMC may determine, AstraZeneca will prepare, in consultation and with input from Akcea, and present to the JCMC, for the JCMC to review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve, an updated U.S. Commercialization Plan and Budget to replace the Interim U.S. Commercialization Plan and Budget. The JSC shall review and determine whether to approve such updated U.S. Commercialization Plan and Budget. The updated U.S. Commercialization Plan and Budget will at all times include: (i) all Commercialization activities to be conducted by each Party for the Licensed Product in the United States, including any post-approval commitments required by the FDA, (ii) a detailed [***] promotional plan for each Licensed Product (which will be consistent with the guidelines in Schedule 3.2.1), (iii) the allocation of responsibilities between the Parties (which allocation will be consistent with Schedule 3.2.1) and the estimated timelines for all activities under the U.S. Commercialization Plan and Budget, and (iv) a written budget for the performance of all activities set forth in the U.S. Commercialization Plan and Budget, in all cases (except for clause (ii)), for [***]; *provided* that [***]. The Parties will use diligent efforts to enable the JSC to approve the comprehensive U.S. Commercialization Plan and Budget described in this Section 3.2.1(b) within [***] after the Closing Date; *provided* that the first comprehensive U.S. Commercialization Plan and Budget will focus primarily on Commercialization of the Licensed Products for [***], and any Commercialization activities with respect to [***] will be included at a high level, with the understanding that AstraZeneca will update the comprehensive U.S. Commercialization Plan and Budget to include additional detail regarding Commercialization of the Licensed Products for [***]. The Interim U.S. Commercialization Plan and Budget will be superseded upon approval of the comprehensive U.S. Commercialization Plan and Budget described in this Section 3.2.1(b).

3.2.2 U.S. Medical Affairs Plan and Budget. Unless and until Akcea exercises the Opt-Out Right in accordance with Section 3.6, the Medical Affairs activities for the Licensed Product in the United States will be governed by a written plan that will include a corresponding budget (such Medical Affairs plan, as it may be modified in accordance with the terms and conditions of this Agreement, the "***U.S. Medical Affairs Plan and Budget***" and the activities set forth in the U.S. Medical Affairs Plan and Budget, together with the activities set forth in the U.S. Commercialization Plan and Budget, the "***Co-Commercialization and Medical Affairs Activities***"). Only activities that are solely or primarily intended for the U.S. will be classified as "U.S. Medical Affairs" activities in the U.S. Medical Affairs Plan and Budget, and [***] will not exercise its final decision-making right in Section 6.6.5(f) to approve a U.S. Medical Affairs Plan and Budget that is inconsistent with the foregoing.

(a) **Interim U.S. Medical Affairs Plan and Budget**. Within [***] after the Closing Date (or longer time period as may be agreed by the Parties), AstraZeneca will prepare, in consultation and with input from Akcea, an interim U.S. Medical Affairs Plan and Budget to govern the Medical Affairs activities for the Licensed Product in the U.S. from the Closing Date through [***] (the "***Interim U.S. Medical Affairs Plan and Budget***"), which plan will contain (i) all Medical Affairs activities to be conducted by each Party for the Licensed Product in the United States from the Closing Date through [***], (ii) the allocation of responsibilities between the Parties (which allocation will be consistent with Schedule 3.2.1), (iii) the estimated timelines for all activities under the Interim U.S. Medical Affairs Plan and Budget, and (iv) a reasonably detailed written budget for the performance of all activities set forth in the Interim U.S. Medical Affairs Plan and Budget. AstraZeneca will present the Interim U.S. Medical Affairs Plan and Budget to the JCMC for the JCMC to review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve the Interim U.S. Medical Affairs Plan and Budget. The JSC shall review and determine whether to approve such Interim U.S. Medical Affairs Plan and Budget. The Interim U.S. Medical Affairs Plan and Budget will be considered the "U.S. Medical Affairs Plan and Budget" (including for purposes of cost-sharing) until a comprehensive U.S. Medical Affairs Plan and Budget is approved by the JSC pursuant to Section 3.2.2(b) (which approval will be memorialized in the minutes of such JSC meeting). The Interim U.S. Medical Affairs Plan and Budget will focus primarily on Medical Affairs activities with respect to the Licensed Products [***], and any Medical Affairs activities with respect to [***] will be included at a high level. Notwithstanding any provision to the contrary in this Agreement, Akcea will have the right to continue conducting any Medical Affairs activities for the Licensed Product in the United States that were ongoing prior to the Closing Date until the JSC approves the Interim U.S. Medical Affairs Plan and Budget; *provided* that (x) upon the reasonable request of AstraZeneca, the Parties will meet to discuss such Medical Affairs activities and Akcea's performance thereof, and (y) Akcea will use reasonable efforts to comply with AstraZeneca's operating policies and processes in the performance of such Medical Affairs activities to the extent (1) such policies and processes (and any updates or changes thereto) are provided reasonably in advance in writing to Akcea and (2) compliance with such policies and processes by Akcea or its Affiliates is reasonably practicable.

(b) **Comprehensive U.S. Medical Affairs Plan and Budget**. At such time as the JCMC may determine, AstraZeneca will prepare, in consultation and with input from Akcea, and present to the JCMC, for the JCMC to review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve, an updated U.S. Medical Affairs Plan and Budget to replace the Interim U.S. Medical Affairs Plan and Budget. The JSC shall review and determine whether to approve such updated U.S. Medical Affairs Plan and Budget. The updated U.S. Medical Affairs Plan and Budget will at all times include: (i) all Medical Affairs activities to be conducted by each Party for the Licensed Product in the United States, (ii) the allocation of responsibilities between the Parties (which allocation will be consistent with Schedule 3.2.1) and the estimated timelines for all activities under the U.S. Medical Affairs Plan and Budget, (iii) the strategy for publications and medical congresses related to the Licensed Product, and (iv) a written budget for the performance of all activities set forth in the U.S. Medical Affairs Plan and Budget, in all cases, for [***]; *provided* that [***]. The first comprehensive U.S. Medical Affairs Plan and Budget will focus primarily on Medical Affairs activities with respect to the Licensed Products [***], and any Medical Affairs activities with respect to [***] will be included at a high level, with the understanding that AstraZeneca will update the comprehensive U.S. Medical Affairs Plan and Budget to include additional detail regarding Medical Affairs activities with respect to the Licensed Products [***]. The Interim U.S. Medical Affairs Plan and Budget will be superseded upon approval of the comprehensive U.S. Medical Affairs Plan and Budget described in this Section 3.2.2(b).

3.2.3 Changes to the U.S. Commercialization Plan and Budget or the U.S. Medical Affairs Plan and Budget.

(a) If a Party wishes to make a change to the U.S. Commercialization Plan and Budget or the U.S. Medical Affairs Plan and Budget, then such Party will submit its proposed change to the JCMC for the JCMC to review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve such change. The JSC shall review and determine whether to approve such change to the U.S. Commercialization Plan and Budget or the U.S. Medical Affairs Plan and Budget, as applicable. Each such update to the U.S. Commercialization Plan and Budget or the U.S. Medical Affairs Plan and Budget will become effective and will supersede the previous U.S. Commercialization Plan and Budget or U.S. Medical Affairs Plan and Budget, as applicable, upon approval thereof by the JSC (which approval will be memorialized in the minutes of such JSC meeting).

(b) For any Calendar Year in a U.S. Commercialization Plan and Budget and U.S. Medical Affairs Plan and Budget (such Calendar Year, the "***Reference Calendar Year***"), if the Senior Officers are unable to agree to, and [***] exercises its final decision-making right in Section 6.6.5(e) or Section 6.6.5(f), as applicable, to approve, an update to the budget for the Reference Calendar Year set forth in any U.S. Commercialization Plan and Budget or U.S. Medical Affairs Plan and Budget, then the Parties' cost-sharing obligations under Section 3.4.1 for such Reference Calendar Year under the U.S. Commercialization Plan and Budget and U.S. Medical Affairs Plan and Budget combined will be [***] (such amount, the "***Cost Sharing Cap***"). Any FTE Costs and Out-of-Pocket Costs incurred for Commercialization or Medical Affairs activities for the Licensed Product in the U.S. in excess of the Cost Sharing Cap for a given Calendar Year will not constitute Eligible Expenses and AstraZeneca will be responsible for all such FTE Costs and Out-of-Pocket Costs. Schedule 3.2.3(b) contains examples of the budgeting and cap mechanism contemplated by this Section 3.2.3(b), which examples are for illustrative purposes only. Notwithstanding the foregoing, if the Parties approve by unanimous Party Vote or by the Senior Officers the budget for the Reference Calendar Year set forth in the U.S. Commercialization Plan and Budget and the U.S. Medical Affairs Plan and Budget when the Reference Calendar Year is the immediately following Calendar Year (e.g., the Parties approve a budget for Calendar Year 2024 in the fourth quarter of 2023), then the provisions of this Section 3.2.3(b) and the Cost Sharing Cap shall not apply.

3.2.4 Co-Commercialization Agreement. Without limiting Section 3.2.1 or Section 3.2.2, prior to [***] performing any marketing or promotional activities for the Licensed Product for the U.S., the Parties shall negotiate in good faith and enter into a co-commercialization agreement to govern the Parties' performance of co-commercialization, which agreement shall contain reasonable and customary terms for similar co-commercialization agreements that are consistent with the terms and conditions of this Agreement, including the U.S. Commercialization Plan and Budget, U.S. Medical Affairs Plan and Budget and Schedule 3.2.1.

3.3 **ROW Commercialization Plan and Updates**. AstraZeneca will have the sole right to Commercialize the Licensed Product in the ROW Territory and will conduct such Commercialization in accordance with a high-level written plan or a comparable document consistent with AstraZeneca's then current internal practices for AstraZeneca's internal programs outlining key aspects of Commercialization activities for such Licensed Product in the ROW Territory (the "***ROW Commercialization Plan***"). The ROW Commercialization Plan will contain high-level information consistent with AstraZeneca's commercialization plans for its similar products at similar stages of commercialization in the same AstraZeneca franchise, including a status update, timelines, goals, and success criteria, but excluding any confidential information of a Third Party that AstraZeneca is prohibited from sharing with Akcea under restrictions imposed by such Third Party (*provided* that AstraZeneca will use Commercially Reasonable Efforts to ensure any agreement specific to the Licensed Compound or Licensed Product entered into after the Closing Date will allow for such sharing with Akcea). No later than [***] prior to the anticipated First Commercial Sale of the Licensed Product in [***], AstraZeneca will prepare the ROW Commercialization Plan and provide the JCMC with copies of such ROW Commercialization Plan to review and discuss; *provided* that the first ROW Commercialization Plan will focus primarily on Commercialization of the Licensed Products in the ROW Territory [***], and any Commercialization activities in the ROW Territory with respect to [***] will be included at a high level, with the understanding that AstraZeneca will update the ROW Commercialization Plan to include additional detail regarding Commercialization of the Licensed Products in the ROW Territory [***]. At least once every [***] during the Term (or more frequently as may be consistent with AstraZeneca's standard practice), AstraZeneca will review and update the ROW Commercialization Plan based on the currently available information and data for the Licensed Product and provide updated copies of such ROW Commercialization Plan to the JCMC for the JCMC to review and discuss. AstraZeneca will [***] any comments provided by Akcea on the ROW Commercialization Plan.

3.4 **Commercialization and Medical Affairs Costs**.

3.4.1 **Shared Commercialization and Medical Affairs Costs**.

(a) **Share Ratios**. The Parties will share the Eligible Commercialization Expenses and the Eligible Medical Affairs Expenses that are reasonably allocable to Commercialization and Medical Affairs activities for Licensed Products for the U.S. prior to the Opt-Out Date, if any, as follows, but subject to the Cost Sharing Cap (if applicable): Akcea will bear [***] and AstraZeneca will bear [***] of all Eligible Commercialization Expenses and Eligible Medical Affairs Expenses for Commercialization and Medical Affairs activities that are expressly classified as "U.S. Commercial" or "U.S. Medical Affairs" activities in the U.S. Commercialization Plan and Budget or the U.S. Medical Affairs Plan and Budget, as applicable; *provided* that Akcea will bear [***] and AstraZeneca will bear [***] of (i) all Eligible Commercialization Expenses incurred in [***] and (ii) Eligible Commercialization Expenses and Eligible Medical Affairs Expenses for Commercialization and Medical Affairs activities that are [***], in the case of clause (ii) that are expressly classified in the U.S. Commercialization Plan and Budget or the U.S. Medical Affairs Plan and Budget, as applicable, as activities that are [***].

(b) **Shared Commercialization and Medical Affairs Costs Payment Reconciliation**. Unless and until the Opt-Out Date occurs (and for the Calendar Quarter in which the Opt-Out Date occurs), the following shall apply:

(i) No later than [***] after the end of each Calendar Quarter, each Party will deliver to the other Party a non-binding estimate that sets forth the Eligible Commercialization Expenses and Eligible Medical Affairs Expenses incurred by or on behalf of such Party during such Calendar Quarter. No later than [***] after the end of each Calendar Quarter, each Party will deliver to the other Party a written report that sets forth in detail the actual Eligible Commercialization Expenses and Eligible Medical Affairs Expenses incurred by or on behalf of such Party during such Calendar Quarter, including a comparison of such Eligible Commercialization Expenses and Eligible Medical Affairs Expenses for a Commercialization or Medical Affairs activity, as applicable, to the amount budgeted for such activity in the U.S. Commercialization Plan and Budget or U.S. Medical Affairs Plan and Budget (the "***Commercialization and Medical Affairs Cost Share Notice***"). Each Party will provide the other Party with supporting documentation of such Eligible Commercialization Expenses and Eligible Medical Affairs Expenses if reasonably requested by the other Party. For each Calendar Quarter, no later than [***] after receipt of the Commercialization and Medical Affairs Cost Share Notice for such Calendar Quarter from each Party, the Party that incurred less than its allocation of Eligible Commercialization Expenses and Eligible Medical Affairs Expenses during such Calendar Quarter will make a balancing payment to the other Party to effect the cost-sharing ratios set forth in Section 3.4.1(a), to the extent the amounts set forth in the Commercialization and Medical Affairs Cost Share Notices are undisputed. Any dispute regarding amounts set forth in a Commercialization and Medical Affairs Cost Share Notice will be promptly referred to the JSC for resolution, and if the JSC determines that any disputed amount should be included in the applicable Commercialization and Medical Affairs Cost Share Notice, the Party that incurred less than its allocation of Eligible Commercialization Expenses and Eligible Medical Affairs Expenses during such Calendar Quarter (taking into account any balancing payments previously made for such Calendar Quarter pursuant to the immediately preceding sentence) will make a balancing payment to the other Party to effect the cost-sharing ratios set forth in Section 3.4.1(a) within [***] of the JSC determination.

3.4.2 **ROW Commercialization Costs**. Except as set forth in Section 3.4.1(a), [***] will be solely responsible for [***] of its costs and expenses incurred in connection with the Commercialization and Medical Affairs activities for the Licensed Product in the ROW Territory.

3.5 **Commercialization and Medical Affairs Reporting**. On a quarterly basis, if a Party is conducting any Commercialization or Medical Affairs activities for the Licensed Product in the Territory, then such Party will, within [***] after the end of each Calendar Quarter, provide to the JCMC for its review and discussion, a high-level report summarizing such Party's and its Affiliates' and Sublicensees' material Commercialization and Medical Affairs activities with respect to the Licensed Product over the prior Calendar Quarter.

3.6 Akcea Opt-Out Right.

3.6.1 Opt-Out Right and Exercise. If Akcea no longer wants to participate in Co-Commercialization and Medical Affairs Activities, it will also have the right to opt-out of its rights and obligations to perform the Co-Commercialization and Medical Affairs Activities and to pay any portion of Eligible Expenses set forth under this Agreement (such right the "***Opt-Out Right***"). Akcea may exercise the Opt-Out Right by providing written notice to AstraZeneca of such election anytime from the Closing Date until (a) [***] (such time period, including any extension as set forth in this Section 3.6.1, the "***First Opt-Out Period***") and (b) [***] (such time period, including any extension as set forth in this Section 3.6.1, the "***Second Opt-Out Period***"). On an Initial Indication-by-Initial Indication basis, promptly after [***], unless Akcea has already exercised its Opt-Out Right, AstraZeneca will prepare and present to the JCMC, for the JCMC to review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve, an updated U.S. Commercialization Plan and Budget and U.S. Medical Affairs Plan and Budget that reflect the Co-Commercialization and Medical Affairs Activities for the Licensed Product in such Initial Indication, which will include AstraZeneca's then most recent forecasted profit and loss model for each Licensed Product for the [***] Calendar Years; *provided* that, for clarity, such profit and loss model shall be for information purposes only and shall not affect the U.S. Commercialization Plan and Budget or the U.S. Medical Affairs Plan and Budget or the financial allocations hereunder. If AstraZeneca fails to provide such updated U.S. Commercialization Plan and Budget and U.S. Medical Affairs Plan and Budget to the JCMC within [***] after [***], then the First Opt-Out Period or Second Opt-Out Period (as applicable) will be extended until [***] after AstraZeneca presents such updated U.S. Commercialization Plan and Budget and such updated U.S. Medical Affairs Plan and Budget to the JCMC.

3.6.2 Effects of Opt-Out.

(a) **In General**. If Akcea exercises the Opt-Out Right during either the First Opt-Out Period or the Second Opt-Out Period pursuant to this Section 3.6, then as of (x) if Akcea provides written notice to AstraZeneca of such election prior to [***] and (y) if Akcea provides written notice to AstraZeneca of such election on or after [***] (the date described in clause (x) or clause (y), as applicable, "***Opt-Out Date***") (*provided* that if Akcea is deemed to exercise the Opt-Out Right pursuant to Section 16.3.4 or Section 17.11.3, the Opt-Out Date shall be the date that AstraZeneca provides written notice thereof to Akcea pursuant to Section 16.3.4 or Section 17.11.3, as applicable), without limiting any other effects of exercise of the Opt-Out Right set forth in this Agreement, the following effects will apply:

(i) Unless otherwise agreed by the Parties, Akcea will no longer have any rights or obligations with respect to, and AstraZeneca will have the sole right to conduct, at its sole cost and expense, all further Development activities for the Licensed Product for the Territory, except that Akcea will continue to conduct any Clinical Trial allocated to Akcea under the Development Plan and Budget that is ongoing as of the Opt-Out Date at AstraZeneca's sole cost and expense for Eligible Development Expenses, until the earlier of Completion of such Clinical Trial or AstraZeneca's request for such Clinical Trial to be transferred to AstraZeneca (which transfer will be at AstraZeneca's sole cost and expense and effectuated on a mutually agreed timeline). The JDC shall review and discuss (but not approve) any further updates or amendments to the Development Plan and Budget, and, notwithstanding Section 2.2.1, any future iterations of the Development Plan and Budget will be consistent with AstraZeneca's then current internal practices for AstraZeneca's internal programs outlining key aspects of the Development of the Licensed Product through all Regulatory Approval and will not need to include a budget;

(ii) the provisions of Section 2.5 (Additional Development) will no longer apply;

(iii) Akcea will no longer have any rights or obligations with respect to, and AstraZeneca will have the sole right to conduct, at its sole cost and expense, all further Medical Affairs activities for the Licensed Product in the Territory;

(iv) Akcea will no longer have any rights or obligations with respect to, and AstraZeneca will have the sole right to conduct, at its sole cost and expense, all further Commercialization activities for the Licensed Product in the Territory;

(v) the provisions of Section 3.2 (U.S. Commercialization Plan and Budget, U.S. Medical Affairs Plan and Budget and Updates) will no longer apply, and the provisions of Section 3.3 (ROW Commercialization Plan and Updates) will apply to the U.S. and the ROW Territory;

(vi) AstraZeneca's reporting obligations under Section 3.5 (Commercialization and Medical Affairs Reporting) will apply to both the U.S. and the ROW Territory on [***] basis (rather than a quarterly basis);

(vii) AstraZeneca will buy, at [***], any API and drug product for the Licensed Product that is required by AstraZeneca to complete such ongoing Clinical Trials for the Licensed Product, if applicable; *provided* that the foregoing shall not affect Akcea's obligations under Section 5.1.1 to Manufacture and supply clinical supply of the Licensed Compound and the Licensed Product through the later of (A) [***] and (B) [***], and at [***] request, Akcea and AstraZeneca shall negotiate in good faith and enter into a supply agreement and quality agreement to govern such supply, which agreements shall contain reasonable and customary terms for similar supply and quality agreements that are not inconsistent with the terms and conditions of this Agreement;

(viii) the licenses granted to Akcea under Section 8.2 will automatically and immediately terminate, except to the extent (and for so long as is) required to perform Development activities pursuant to Section 3.6.2(a)(i) and to Manufacture and supply clinical supply of the Licensed Compound and the Licensed Product in accordance with Section 5.1.1;

(ix) the provisions of Section 5.4 (Capital Expenditures) will no longer apply;

(x) Akcea will not be responsible for any Eligible Expenses to the extent reasonably allocable to Exploitation of the Licensed Product from and after the Opt-Out Date; and

(xi) AstraZeneca will no longer be responsible for [***] achieved after the Opt-Out Date.

(b) **Opt-Out Economics**.

(i) **Scenario One**. Subject to the remainder of this Section 3.6.2(b), if Akcea exercises the Opt-Out Right (including if Akcea is deemed to exercise the Opt-Out Right pursuant to Section 16.3.4 or Section 17.11.3), then, in addition to the effects set forth in Section 3.6.2(a), subject to Section 3.6.2(b)(ii), AstraZeneca will pay Akcea royalties at royalty rates that are agreed to by the Parties within [***] of such exercise (such royalty rates, "***Opt-Out Scenario One Royalty Rates***") on Net Sales in the U.S. from and after the Opt-Out Date ("***Opt-Out Scenario One Royalties***"). Subject to Section 17.11.3, such Opt-Out Scenario One Royalty Rates will be determined by the Parties to equate to [***] of the estimated average per unit U.S. operating profit with respect to the Licensed Product(s) from the First Commercial Sale of the Licensed Product through the anticipated expiration of the Royalty Term (taking into account the effects of any Patent Term Extensions) in the U.S. The "U.S. operating profit" will be determined consistently with AstraZeneca's Accounting Standards (as such Accounting Standards are applied consistently across AstraZeneca's products) and will not take into account any payments owed to Akcea under this Agreement. To facilitate the negotiation of such Opt-Out Scenario One Royalty Rates, AstraZeneca will provide, within [***] after the date that Akcea exercises the Opt-Out Right, Akcea with its [***]. For clarity, the Opt-Out Scenario One Royalty Rates will be determined one time (within [***] of Akcea's exercise of the Opt-Out Right, subject to any extension pursuant to Section 3.6.2(b)(ii)) and shall not be adjusted or renegotiated after such Opt-Out Scenario One Royalty Rates are agreed. If the Parties agree on the Opt-Out Scenario One Royalty Rates, then (A) except in the case of a deemed exercise of the Opt-Out Right under Section 16.3.4 or Section 17.11.3, AstraZeneca will reimburse Akcea for [***] of Akcea's share of the Eligible Expenses incurred and previously reconciled pursuant to Section 2.4.1, Section 3.4.1 and Section 11.10, as applicable through the Opt-Out Date, which reimbursement shall be made within [***] after the Parties agree on the Opt-Out Scenario One Royalty Rates, (B) AstraZeneca will pay Akcea the Opt-Out Scenario One Royalties on Net Sales of each Licensed Product from and after the Opt-Out Date until the expiration of the Royalty Term for such Licensed Product in the U.S., and (C) AstraZeneca will provide reports and payments to Akcea consistent with Section 11.7.

(ii) **Scenario Two**. If the Parties, acting reasonably and in good faith, fail to agree on the Opt-Out Scenario One Royalty Rates within [***] after the date that Akcea exercises the Opt-Out Right (*provided* that if the Parties are still negotiating in good faith at the conclusion of such [***] period, then such negotiation period for the Opt-Out Scenario One Royalty Rates will be extended by an additional [***]), then, in addition to the effects set forth in Section 3.6.2(a), AstraZeneca will instead pay Akcea royalties on the aggregate Net Sales resulting from the sale of each Licensed Product in the U.S. during each Calendar Year from and after the Opt-Out Date during the Royalty Term at [***] pursuant to Section [***].

3.6.3 Effect of Not Opting-Out. If Akcea does not exercise its Opt-Out Right prior to expiration of the Second Opt-Out Period, then Akcea will no longer have the Opt-Out Right except as set forth in Section 16.3.4 and Section 17.11.3.

ARTICLE 4
REGULATORY

4.1 Regulatory Strategy. The RWG will develop the overall regulatory strategy through [***] in each of the Initial Indications (the "***Regulatory Strategy***"), which Regulatory Strategy shall be submitted to the JDC for review and approval as part of the Development Plan and Budget. The Regulatory Strategy shall include, for each Licensed Product, guidance and strategies for high-level documents, statistical analysis plans, clinical study reports, quality strategy pre- and post-Regulatory Approval and other materials to allow for the preparation and compilation of Regulatory Filings in both of the Initial Indications in the Territory. All Regulatory Filings (including Regulatory Approval Applications) for the treatment of the Initial Indications will be consistent with the Regulatory Strategy.

4.2 Responsibility for Regulatory Filings and Ownership of Regulatory Materials.

4.2.1 In the U.S. and Canada.

(a) **PN**. Unless and until responsibility is transferred to AstraZeneca in accordance with this Section 4.2.1(a), Akcea will be responsible for (i) the Regulatory Filings to support the Clinical Trials that are ongoing as of the Execution Date for the Licensed Product for the treatment of PN and (ii) the Regulatory Filings and Regulatory Approval Applications for the Licensed Product for the treatment of PN in the U.S. and Canada until receipt of Regulatory Approval of the Licensed Product for the treatment of PN. During the period in which Akcea is responsible for such Regulatory Filings to support such Clinical Trials and such other Regulatory Filings and Regulatory Approval Applications for the Licensed Product for the treatment of PN, Akcea will closely collaborate with AstraZeneca and provide AstraZeneca, through its representatives on the RWG, the right to review and approve (1) [***] and (2) [***]. Any disagreement in the RWG will be escalated to the JDC for review and decision making. As soon as reasonably practicable after Regulatory Approval in each of the U.S. and Canada for the Licensed Product for the treatment of PN, Akcea and its Affiliates will transfer and assign to AstraZeneca, at [***] cost, the Regulatory Filings (including the IND, NDA (or its Canadian equivalent)), other Regulatory Approvals and all related documentation (including IND/CTA sequences, briefing documents, correspondence from/to FDA and Health Canada) for the U.S. or Canada, as applicable, related to the Licensed Product, *except*, with respect to Regulatory Filings for Clinical Trials that are ongoing as of the Execution Date for the Licensed Product for the treatment of CM, such Regulatory Filings and all related documentation will be retained by Akcea to the extent required to perform Akcea's obligations in Section 4.2.1(b). Notwithstanding the foregoing, AstraZeneca will have the right, upon written notice to Akcea, to assume responsibility for (x) the Regulatory Filings (including, for clarity, the IND) to support the Clinical Trials that are ongoing as of the Execution Date for the Licensed Product for the treatment of PN and (y) the Regulatory Filings and Regulatory Approval Applications for the Licensed Product for the treatment of PN in the U.S. and Canada, at any time after the Closing Date but no later than receipt of Regulatory Approval in each of the U.S. and Canada for the Licensed Product for the treatment of PN. If AstraZeneca exercises such right, then as soon as practicable following such exercise, Akcea will transfer to AstraZeneca (and AstraZeneca will assume) such Regulatory Filings (including, for clarity, the IND) and Regulatory Approval Applications and, as soon as practicable, notwithstanding Section 2.2.2, AstraZeneca will assume sponsorship and responsibility for conducting any Clinical Trials that are governed by a Regulatory Filing transferred to AstraZeneca under this Section 4.2.1(a).

(b) **CM**. Unless and until responsibility is transferred to AstraZeneca in accordance with this Section 4.2.1(b), Akcea will retain regulatory responsibility for Regulatory Filings to support the Clinical Trials that are ongoing as of the Execution Date for the Licensed Product for the treatment of CM, and, promptly following the Completion of all such Clinical Trials, Akcea will assign the Regulatory Filings, Regulatory Approvals and all related documentation (including IND/CTA sequences, briefing documents, correspondence from/to FDA and any other Regulatory Authority) related to the Licensed Product for the treatment of CM to AstraZeneca. During the period in which Akcea is responsible for Regulatory Filings to support such Clinical Trials, Akcea will closely collaborate with AstraZeneca and provide AstraZeneca, through its representatives on the RWG, the right to review and approve (i) [***] and (ii) [***]. Any disagreement at the RWG will be escalated to the JDC for review and decision making. Notwithstanding the foregoing, AstraZeneca will have the right to assume responsibility for such Regulatory Filings (including, for clarity, the IND) to support such Clinical Trials that are ongoing as of the Execution Date for the Licensed Product for the treatment of CM, at any time after the Closing Date but no later than Completion of all such Clinical Trials. If AstraZeneca exercises such right, then as soon as practicable following such exercise Akcea will transfer to AstraZeneca (and AstraZeneca will assume) such Regulatory Filings (including, for clarity, the IND) and Regulatory Approval Applications and, as soon as practicable, notwithstanding Section 2.2.2, AstraZeneca will assume sponsorship and responsibility for conducting any Clinical Trials that are governed by a Regulatory Filing transferred to AstraZeneca under this Section 4.2.1(b).

4.2.2 **In the EU**. Akcea will be responsible for initial discussions with the EMA and MHRA regarding the path for Regulatory Approval for the Licensed Product for the treatment of [***], and will provide AstraZeneca, through its representatives on the RWG, the right to review and approve (a) [***] and (b) [***]. Any disagreement in the RWG will be escalated to the JDC for review and decision making. Prior to submission of the Regulatory Approval Application to the EMA or MHRA for the Licensed Product for the treatment of [***], Akcea will assign all Regulatory Filings, Regulatory Approvals and all related documentation (including the applicable IND and MAA (or their equivalent), IND/CTA sequences, briefing documents, correspondence from/to FDA and any other Regulatory Authority) for the EU to AstraZeneca. As between the Parties, AstraZeneca will be responsible, in accordance with the Development Plan and Budget and to the extent consistent with its obligations in Section 2.1, for filing and holding the Regulatory Filings and Regulatory Approvals for the Licensed Product for the treatment of the Initial Indications and any other Indications in the EU.

4.2.3 **Other**. Except as otherwise provided in Section 4.1, Section 4.2.1 and Section 4.2.2, as between the Parties, AstraZeneca will have the sole right and will bear all expense for (a) determining the regulatory plans and strategies for the Licensed Product, (b) making all Regulatory Filings with respect to the Licensed Product, and (c) obtaining and maintaining Regulatory Approvals, in each case consistent with the Regulatory Strategy.

4.3 Regulatory Cooperation.

4.3.1 Regulatory Owner Responsibilities. Subject to applicable Law and this Section 4.3, the Party responsible for filing and holding Regulatory Filings and Regulatory Approvals in a particular territory for a particular Licensed Product (if applicable, in a particular Indication) in accordance with Section 4.2 (the "***Regulatory Owner***") will oversee, monitor and manage all regulatory interactions, communications and filings with, and submissions to, Regulatory Authorities in connection with such Regulatory Filings. During the period in which Akcea is the Regulatory Owner in any country, each Party will assign a Global Regulatory Affairs lead to the Licensed Product, and the Akcea Global Regulatory Affairs Lead for the Licensed Product will work in regular contact with the AstraZeneca Global Regulatory Affairs Lead and provide AstraZeneca, through its representatives on the RWG, the right to review and [***] major documents that are submitted by Akcea to Regulatory Authorities in connection with such Regulatory Filings. Any disagreement in the RWG will be escalated to the JDC for review and decision making.

4.3.2 Regulatory Submissions and Correspondence. Subject to applicable Law, the Party that is not the Regulatory Owner will have the right to attend, as a participant, all material meetings, conferences and discussions by the Regulatory Owner or its Affiliate with Regulatory Authorities pertaining to the Development or Regulatory Approval of the Licensed Product in [***]. The Regulatory Owner will provide the other Party with reasonable advance notice of all such interactions and will provide advance copies of all related documents and other relevant information relating to such interactions in [***]. In addition, Akcea will provide the RWG with advance drafts of any Regulatory Filings and any material documents or other material correspondence pertaining to Regulatory Approvals for the Licensed Products that Akcea plans to submit to any Regulatory Authority in accordance with Section 4.2 for the RWG to review, discuss, and [***]. With respect to each Party's obligation to provide advance copies of Regulatory Filings and correspondences in the preceding sentences, (a) for Regulatory Approval Applications, the Parties will agree on a timeline for review of advance drafts and each Party will use commercially reasonable efforts to comply with such timeline and (b) for all other material regulatory submissions and correspondences, each Party will provide advance copies at least [***] prior to submission (unless a shorter time frame is necessary to comply with the requests or requirements of any applicable Regulatory Authority or under any applicable Law). Each Party will provide the other Party with copies of all material submissions it makes to, and all material correspondence it receives from, a Regulatory Authority pertaining to Regulatory Approvals for the Licensed Product in [***].

4.3.3 Assistance. The Parties will cooperate with each other to achieve the regulatory objectives contemplated herein in a timely, accurate, and responsive manner. The non-Regulatory Owner will use reasonable efforts to assist the Regulatory Owner, including by meeting with the Regulatory Owner to prepare Regulatory Filings and other documents to be filed, providing access to relevant data and information (including relevant safety data) and addressing requests from Regulatory Authorities, in each case, in order for such Regulatory Owner to obtain and maintain each applicable Regulatory Approval for the Licensed Product in the Territory. Without limiting the foregoing, Akcea will provide AstraZeneca with the support necessary or reasonably requested by AstraZeneca to obtain and maintain Regulatory Approvals for the Licensed Product in [***], including by drafting provisions of any Regulatory Filing, answering questions from Regulatory Authorities with respect to the Licensed Product and attending any meetings with Regulatory Authorities, in each case, at AstraZeneca's request and, with respect to support requested by AstraZeneca, at [***].

4.3.4 **Global Regulatory Coordination**. The Parties will cooperate to harmonize Regulatory Filings and regulatory activities in the U.S. with Regulatory Filings and regulatory activities outside of the U.S. for the Licensed Product with respect to [***], consistent with the Regulatory Strategy. To the extent practicable, the data and information and presentation of information will be consistent across Regulatory Filings made in the U.S. and Regulatory Filings made outside of the U.S.

4.4 **Class Generic Claims for the Licensed Product**. To the extent AstraZeneca intends to make any claims in a Licensed Product label or Regulatory Filing that are class generic to ASOs or any of Akcea's technology incorporated into a Licensed Product, AstraZeneca will provide such claims and Regulatory Filings to Akcea in advance and will [***] any proposals and comments made by Akcea.

4.5 **Recalls**. The applicable Regulatory Owner will determine whether to initiate any recall, withdrawal, or stock recovery of any Licensed Product in any country or jurisdiction in the Territory; *provided* that the Regulatory Owner will implement any recall, withdrawal, or stock recovery that is required by applicable Law or a Regulatory Authority, and in each case, consistent with the requirements of applicable Law or such Regulatory Authority. Each Party will notify the other Party promptly upon its determination that any event, incident or circumstance has occurred that may result in the need for a recall, market withdrawal or stock recovery of a Licensed Product (but in no event later than 48 hours and in all cases prior to the execution of such recall, market withdrawal or stock recovery) and will consider the comments of the other Party in good faith. For all recalls, market withdrawals and stock recoveries that are taken, the Regulatory Owner will be responsible for execution, and the other Party will reasonably cooperate in all such efforts.

4.6 **Adverse Event Reporting; Global Safety Database**.

4.6.1 The then-current holder of the IND with respect to a given Clinical Trial will have Territory-wide responsibility for pharmacovigilance with respect to such Clinical Trial consistent with the Regulatory Strategy, including for all reportable events associated with such Clinical Trial to the applicable Regulatory Authorities. Each Party will use reasonable efforts to complete the transfer to AstraZeneca of the global safety database and datasets for the Licensed Product in the Territory promptly following the first Regulatory Approval for the Licensed Product (or, if earlier, the date on which AstraZeneca becomes the Regulatory Owner for the Licensed Product in any Major Market) and, following such transfer, AstraZeneca will have the sole right and responsibility for holding and maintaining such global safety database.

4.6.2 Promptly after the Closing Date, the Parties will negotiate in good faith and enter into a mutually-agreed safety data exchange agreement (the "***SDEA***") (which must be executed prior to the transfer of any IND or Regulatory Approval or the global safety database and datasets), which agreement will provide for the responsibilities of the Parties related to the management of safety information related to the Licensed Product, including any such information received by either Party or its Affiliates from any Third Party (including reports from Clinical Trials, health care personnel (HCP) and customers). It is understood that each Party and its Affiliates and licensees or sublicensees will disclose such information necessary to comply with applicable Laws as well as requirements of any applicable Regulatory Authority. The SDEA will remain in effect for so long as the exchange of safety information is required by Law.

4.6.3 Akcea's Internal Antisense Safety Database.

(a) Akcea 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 "***Akcea Internal ASO Safety Database***"). In an effort to maximize understanding of the safety profile and pharmacokinetics of Akcea compounds, AstraZeneca will cooperate in connection with populating the Akcea Internal ASO Safety Database, *provided* that AstraZeneca's obligations pursuant to this Section 4.6.3 are subject to applicable Law and in particular AstraZeneca will not be required to disclose any information in contravention of applicable Law relating to data privacy. To the extent collected by AstraZeneca and, in the form in which AstraZeneca uses/stores such information for its own purposes, AstraZeneca will provide Akcea with material information concerning toxicology, pharmacokinetics, safety pharmacology study(ies), serious adverse events and other safety information related to the Licensed Product as soon as practicable following the date such information is available to AstraZeneca (but not later than [***] after AstraZeneca's receipt of such information). In connection with any reported serious adverse event, AstraZeneca will provide Akcea with all serious adverse event reports, including initial, interim, follow-up, amended, and final reports. In addition, with respect to the Licensed Product, AstraZeneca will provide Akcea with copies of annual safety updates filed with each IND and the safety sections of any final Clinical Trial reports. Furthermore, AstraZeneca will promptly provide Akcea with any supporting data and answer any follow-up questions reasonably requested by Akcea to conduct analyses to keep Akcea and its partners informed regarding class generic properties of ASOs, including with respect to safety. All such information disclosed by AstraZeneca to Akcea will be AstraZeneca Confidential Information; *provided*, *however*, that so long as Akcea does not disclose the identity of the Licensed Product (or the Licensed Compound) or AstraZeneca's identity, Akcea may disclose any such AstraZeneca Confidential Information to Regulatory Authorities and Akcea's other partners pursuant to Section 4.6.3(b) below if such information is regarding class generic properties of ASOs and, with respect to Akcea's partners, such partners have agreed to a similar provision permitting the disclosure of their Confidential Information relating to ASOs to Akcea's partners. AstraZeneca will deliver all such information to Akcea for the Akcea Internal ASO Safety Database to Akcea Therapeutics, Inc., 2855 Gazelle Court, Carlsbad, CA 92010, Attention: Chief Medical Officer (or to such other address/contact designated in writing by Akcea). AstraZeneca will also cause its Affiliates and its and their Sublicensees to comply with this Section 4.6.3(a).

(b) From time to time, Akcea utilizes the information in the Akcea Internal ASO Safety Database to conduct analyses to keep Akcea and its partners (including its Affiliates' partners) informed regarding class generic properties of ASOs, including with respect to safety. As such, if and when Akcea identifies safety or other related issues that may be relevant to the Licensed Product (including any potential class-related toxicity), Akcea will promptly inform AstraZeneca of such issues and provide the data supporting Akcea's conclusions.

ARTICLE 5
MANUFACTURING AND SUPPLY

5.1 Supply of the Licensed Products.

5.1.1 Manufacturing Responsibility for Ongoing Clinical Trials. Akcea will, itself or with or through an Affiliate or CMO, Manufacture and supply clinical supply of the Licensed Compound and the Licensed Product for the Parties' Development activities under this Agreement in accordance with the Development Plan and Budget through the later of (a) [***] and (b) [***]. Akcea will not make any material changes to the Manufacturing process for the Licensed Compound or the Licensed Product, nor any changes to the applicable CMOs conducting such Manufacturing activities, without the prior written consent of AstraZeneca.

5.1.2 Additional Clinical and Commercial Manufacturing Responsibility. From and after completion of the activities set forth in the Manufacturing Transition Plan, except as otherwise expressly set forth in Section 5.1.1, this Section 5.1.2 or as otherwise agreed by the Parties, AstraZeneca will be solely responsible for the Manufacture of the Licensed Compound and Licensed Product, including Manufacture of registration batches, stability batches and commercial batches, and management of the overall manufacturing strategy and tactics, formulation, CMO selection for API and finished Licensed Product and associated audits; *provided*, that (a) [***], (b) [***] and (c) Akcea will be responsible for managing the process performance qualification batches for API and finished Licensed Product for such Authorized CMOs for the Initial Indications in the United States and Canada.

5.1.3 Existing Inventory. If there is any clinical supply of the Licensed Product or Licensed Product Manufactured pursuant to process performance qualification batches to support Regulatory Approval, in each case, remaining after Regulatory Approval for the Licensed Product that is suitable for commercial sale (including appropriate shelf life), then AstraZeneca will use reasonable efforts to purchase such Licensed Product at: (a) [***] and (b) [***].

5.2 Manufacturing Transition Plan.

5.2.1 As soon as reasonably practicable but in any event within [***] after the Closing Date, the Parties will establish a plan sufficient to enable AstraZeneca or its designee to manufacture the amount of Licensed Compound and Licensed Product necessary for the Parties to conduct the activities as contemplated by the Development Plan and Budget, the U.S. Commercialization Plan and Budget and the ROW Commercialization Plan (or drafts thereof if any such plan has yet to be finalized or approved) (the "***Manufacturing Transition Plan***"), which Manufacturing Transition Plan will (a) contemplate that Akcea will continue to Manufacture and supply the clinical supply of the Licensed Compound and the Licensed Product through the completion of all Clinical Trials that are ongoing as of the Execution Date pursuant to Section 5.1.1 and will manage the process performance qualification batches for API and finished Licensed Product, and AstraZeneca will be responsible for the Manufacture and supply of all commercial supply of Licensed Compound and Licensed Product, and (b) provide for a smooth transition to AstraZeneca between the clinical and commercial supply phases, including any gaps therein. Pursuant to the process and timelines set forth in the Manufacturing Transition Plan (and in any event within the later of (i) [***] or (ii) [***], Akcea will assign to AstraZeneca any agreements with Akcea's CMOs for the Licensed Product, unless [***], in which case [***].

5.2.2 If, despite AstraZeneca's Commercially Reasonable Efforts, the [***] does not occur or is not sufficient for AstraZeneca or its designee to manufacture the Licensed Compound and Licensed Product (either at the time of [***]), then, at a time and to the extent requested by AstraZeneca, the Parties will amend the Manufacturing Transition Plan to include, and Akcea shall conduct, a manufacturing technology transfer to AstraZeneca or its Affiliate or any designee approved by Akcea in accordance with Section 7.2.1 (if applicable), including, to the extent not already transferred to AstraZeneca, the transfer of (a) the manufacturing processes for Licensed Compounds and all Know-How and materials with respect thereto (including all raw material specifications, quality and in process testing and data, release testing and data, and stability data), in each case, in Akcea's or its Affiliates' possession or control, including any such Know-How and materials maintained by Akcea's Third Party providers, that Akcea has the right to transfer, (b) all other Akcea Manufacturing and Analytical Know-How that [***] to Manufacture the Licensed Compounds, (c) all inventory of Licensed Compounds, drug substance and drug product in Akcea's possession or control and (d) reasonable amounts of analytical reagents and raw materials that are reasonably requested by AstraZeneca, in Akcea's possession or control and, in the case of analytical reagents and raw materials being used in connection with other Akcea programs, *provided* that any amounts requested by AstraZeneca take into account Akcea's continuing needs for its other programs. Notwithstanding any provision to the contrary in this Agreement, Akcea will only be required to conduct one manufacturing technology transfer pursuant to this Section 5.2.2 (*i.e.*, only one additional manufacturing technology transfer in addition to the initial manufacturing technology transfer set forth in Section 5.2.1), which manufacturing technology transfer must be to either AstraZeneca, its Affiliate or a single designee approved by Akcea in accordance with Section 7.2.1 (if applicable).

5.3 Manufacturing Improvements.

5.3.1 Akcea Improvements.

(a) **Disclosure**. During the Term, Akcea shall promptly disclose to AstraZeneca (i) all modifications, enhancements and improvements to the processes for the Manufacture of the Licensed Compound and Licensed Product and (ii) [***], in each case ((i) and (ii)) conceived, discovered, invented or created or acquired (whether by license, option, acquisition or otherwise) or otherwise Controlled by or on behalf of Akcea or any of its Affiliates that [***] to Manufacture the Licensed Products ((i) and (ii) together with the Patent Rights Covering the foregoing, "***Akcea Manufacturing Improvements***"). At AstraZeneca's request, Akcea shall provide AstraZeneca with reasonable assistance to enable AstraZeneca (or its Affiliate or CMO, as applicable) to implement such modifications, enhancements and improvements with respect to the Licensed Compound and Licensed Product, and AstraZeneca shall reimburse Akcea for the [***] incurred by Akcea with respect to such assistance.

(b) **Third Party Agreements**. To the extent that any Akcea Manufacturing Improvement is in-licensed or acquired by Akcea or any of its Affiliates (any such agreement, an "***Akcea Manufacturing Improvement In-License***"), (i) Akcea shall provide a copy of such Akcea Manufacturing Improvement In-License to AstraZeneca (which copy may be redacted as necessary to comply with its obligations of confidentiality to the counterparty provided that such redactions do not undermine AstraZeneca's ability to comply with such Akcea Manufacturing Improvement In-License or understand the [***] applicable to AstraZeneca), and any license to AstraZeneca under such Akcea Manufacturing Improvements pursuant to Section 8.1 shall be subject to the terms and conditions of such Akcea Manufacturing Improvement In-License, (ii) AstraZeneca shall (A) provide the necessary reporting information to Akcea in sufficient time as reasonably requested by Akcea to enable Akcea to comply with its obligations under such Akcea Manufacturing Improvement In-License and Akcea's obligation to [***] pursuant to clause (B), (B) [***] and (C) not, and shall cause its Affiliates and Sublicensees not to, take or fail to take any action if doing so (or not doing so) would cause Akcea to be in breach of any such Akcea Manufacturing Improvement In-License to the extent that any applicable obligations have been disclosed to AstraZeneca and (iii) [***]. Neither Akcea nor its Affiliates will amend, modify, terminate, or waive any rights under any Akcea Manufacturing Improvement In-License in a manner that would adversely affect AstraZeneca's rights or obligations under this Section 5.3.1 without AstraZeneca's prior written consent. Neither Akcea nor its Affiliates will commit any acts or permit the occurrence of any omissions that would cause or result in the termination of any Akcea Manufacturing Improvement In-License which termination would adversely affect AstraZeneca's rights or obligations under this Section 5.3.1, without AstraZeneca's prior written consent.

(c) **Right to Terminate**. AstraZeneca may terminate its license under all or any portion of any Akcea Manufacturing Improvements at any time by providing written notice to Akcea and upon Akcea's receipt of such notice the applicable Know-How or Patent Rights shall be excluded from Licensed Technology and from the licenses granted to AstraZeneca pursuant to Section 8.1.

5.3.2 AstraZeneca Improvements.

(a) **Grant to Akcea**. Subject to Section 8.1, Section 5.3.2(b) and Section 5.3.2(c), AstraZeneca hereby grants to Akcea a non-exclusive, royalty-free, perpetual, irrevocable non-transferable, non-sublicensable (except in accordance with the following proviso) license under all modifications, enhancements and improvements to the processes for the Manufacture of the Licensed Compound and Licensed Product that were transferred to AstraZeneca pursuant to Section 5.2 and Section 5.3.1 made under this Agreement during the Term and any Patent Rights that claim any such modifications, enhancements or improvements to the extent such modifications, enhancements, improvements or Patent Rights, as applicable, are Controlled by AstraZeneca (collectively, "***AstraZeneca Manufacturing Improvements***") for all Manufacturing purposes other than in a manner that would violate the exclusivity obligations in Section 9.2 or the exclusive licenses granted by Akcea to AstraZeneca under this Agreement; *provided*, *however*, that Akcea shall not practice or use any AstraZeneca Manufacturing Improvements for the benefit of any Affiliate or Third Party, or grant any Affiliate or Third Party a sublicense under any AstraZeneca Manufacturing Improvements, in either case, unless Akcea has the right to grant AstraZeneca a (sub)license (with the right to sublicense through multiple tiers) with respect to all modifications, enhancements and improvements to (i) Akcea's or its Affiliates' Manufacturing processes or any portion therefor [***] in the Manufacture of the Licensed Product [***] and (ii) AstraZeneca Manufacturing Improvements, in each case, ((i) and (ii)), that are conceived, discovered, invented or created or acquired (whether by license, option, acquisition or otherwise) or otherwise controlled by such Affiliate or Third Party, as applicable. During the Term, AstraZeneca will promptly disclose to Akcea all AstraZeneca Manufacturing Improvements.

(b) **Third Party Agreements**. To the extent that any AstraZeneca Manufacturing Improvement is in-licensed or acquired by AstraZeneca or any of its Affiliates (any such agreement, an "***AstraZeneca Manufacturing Improvement In-License***"), (i) AstraZeneca shall provide a copy of such AstraZeneca Manufacturing Improvement In-License to Akcea (which copy may be redacted as necessary to comply with its obligations of confidentiality to the counterparty provided that such redactions do not undermine Akcea's ability to comply with such AstraZeneca Manufacturing Improvement In-License or understand [***]), and any license to Akcea under such AstraZeneca Manufacturing Improvements pursuant to Section 5.3.2(a) shall be subject to the terms and conditions of such AstraZeneca Manufacturing Improvement In-License, (ii) Akcea shall (A) provide the necessary reporting information to AstraZeneca in sufficient time as reasonably requested by AstraZeneca to enable AstraZeneca to comply with its obligations under such AstraZeneca Manufacturing Improvement In-License and AstraZeneca's obligation to [***] pursuant to clause (B), (B) [***] and (C) not, and shall cause its Affiliates and (sub)licensees not to, take or fail to take any action if doing so (or not doing so) would cause AstraZeneca to be in breach of any such AstraZeneca Manufacturing Improvement In-License to the extent that any applicable obligations have been disclosed to Akcea and (iii) [***]. Neither AstraZeneca nor its Affiliates will amend, modify, terminate, or waive any rights under any AstraZeneca Manufacturing Improvement In-License in a manner that would adversely affect Akcea's rights or obligations under this Section 5.3.2 without Akcea's prior written consent. Neither AstraZeneca nor its Affiliates will commit any acts or permit the occurrence of any omissions that would cause or result in the termination of any AstraZeneca Manufacturing Improvement In-License which termination would adversely affect Akcea's rights or obligations under this Section 5.3.2, without Akcea's prior written consent.

(c) **Right to Terminate**. Akcea may terminate its license under all or any portion of any AstraZeneca Manufacturing Improvements at any time by providing written notice to AstraZeneca and upon AstraZeneca's receipt of such notice the applicable Know-How or Patent Rights shall be excluded from AstraZeneca Manufacturing Improvements and from the licenses granted to Akcea pursuant to Section 5.3.2(a). AstraZeneca shall have the right to terminate Akcea's rights under Section 5.3.2(a), on written notice to Akcea, if Akcea breaches its obligations under the proviso set forth therein or under Section 5.3.2(b) and does not cure such breach within [***] after written notice from AstraZeneca of such breach.

5.4 **Capital Expenditures**. Unless and until the Opt-Out Date occurs, if AstraZeneca [***], AstraZeneca shall [***]. If, [***]. For clarity, the foregoing sharing shall not include [***].

ARTICLE 6
GOVERNANCE

6.1 Joint Steering Committee.

6.1.1 Establishment of Joint Steering Committee. Within [***] of the Closing Date, the Parties shall establish a Joint Steering Committee (the "***Joint Steering Committee***" or "***JSC***") to oversee and coordinate the Development, Manufacturing, Commercialization and other Exploitation activities with respect to the Licensed Product for the United States under this Agreement and to share information between the Parties regarding the Development, Manufacturing, Commercialization and other Exploitation activities with respect to the Licensed Product for the ROW Territory under this Agreement. The JSC will consist of an appropriate number of representatives as may be agreed upon by the Parties, with an equal number of representatives designated by each of the Parties. The initial members of the JSC will be nominated by the Parties promptly following the Closing Date. Such representatives shall be individuals suitable in seniority and experience and having sufficient authority to make decisions of the JSC with respect to matters within the scope of the JSC's responsibilities. The JSC shall operate in accordance with the provisions of this Article 6, and shall have no authority to alter, amend or waive the terms and conditions of this Agreement. A Party may change one or more of its representatives serving on the JSC at any time upon written notice to the other Parties, *provided* that such replacement satisfies the requirements set forth above in this Section 6.1.1.

6.1.2 Responsibilities of JSC. The JSC shall perform the following functions:

(a) oversee the overall strategic relationship between the Parties as described in Section 6.1.1;

(b) review and discuss any potential AstraZeneca Third Party Product-Specific License, as described in Section 11.8.2(b);

(c) review and discuss any results, information, analyses, reports and recommendations submitted by the JDC, JCMC or any other Subcommittees, including any drafts of, or updates or changes to, the Development Plan and Budget (including any Additional Development Proposals), the U.S. Commercialization Plan and Budget (including, for clarity, the Interim U.S. Commercialization Plan and Budget) and U.S. Medical Affairs Plan and Budget (including, for clarity, the Interim U.S. Medical Affairs Plan and Budget), and make decisions or provide approvals with respect thereto as provided in Article 2 and Article 3;

(d) review, discuss and approve any Allowable Overruns described in clause (b) of the definition thereof;

(e) review, discuss and resolve any issues escalated to the JSC by any of the Subcommittees; and

(f) perform such other functions as are specifically designated for the JSC in this Agreement or that the Parties mutually agree in writing to refer to the JSC.

6.1.3 JSC Meetings; Minutes.

(a) The JSC will meet in person, by videoconference or by teleconference at least once each Calendar Quarter, unless otherwise agreed by the Parties, on such dates and at such times and places as agreed to by the members of the JSC. Each Party will be responsible for its own expenses relating to attendance at, or participation in, JSC meetings. In addition to scheduled meetings, at any Party's reasonable request, the JSC may meet (including by videoconference or teleconference) upon [***] prior written notice on an ad-hoc basis to address any urgent matters that arise with respect to the Development, Manufacturing, Commercialization or other Exploitation of the Licensed Product. Each Party will ensure that its representatives at such meetings are officers or employees of such Party having sufficient seniority within the applicable Party to make decisions within the purview of the JSC.

(b) The Alliance Managers or their designees will provide the members of the JSC with draft written minutes for approval from each meeting within [***] after each such meeting. The JSC will approve the minutes from a meeting (with each Party's representatives on the JSC collectively having one vote) within [***] after receiving such minutes. The results, reports, analyses and other information regarding the Licensed Product disclosed by one Party to the other Parties through the JSC constitute Confidential Information of both Parties and may be used only in accordance with the rights granted and other terms and conditions under this Agreement. Any reports of the JSC may take the form of and be recorded in minutes of the meetings of the Parties as contemplated under this Section 6.1.3(b), including copies of any slides relating to the results and presented at such meetings.

6.2 Subcommittees. The JDC and the JCMC will be established as subcommittees to the JSC pursuant to Section 6.3 and Section 6.4, respectively, and the JSC may establish such other subcommittees or working groups as may be necessary or desirable to facilitate the activities under this Agreement (each a "***Subcommittee***"). The JSC will delegate such specifically-defined duties as the JSC deems appropriate to any such Subcommittee. Each Subcommittee and its activities will be subject to the oversight of, and will report to, the JSC. No Subcommittee will have authorities that exceed the authorities specified for the JSC, the JDC, or the JCMC in this Article 6. Any disagreement between the representatives of the Parties on a Subcommittee will be referred to the JSC for resolution in accordance with Section 6.6.

6.3 Joint Development Committee.

6.3.1 Establishment of Joint Development Committee. Within [***] of the Closing Date, the Parties shall establish a joint development committee (the "***Joint Development Committee***" or "***JDC***") to oversee and coordinate the Clinical Trials ongoing as of the Execution Date and Development of the Licensed Products in the United States under this Agreement and to share information between the Parties regarding the Development of the Licensed Products in the ROW Territory under this Agreement. The JDC will consist of an appropriate number of representatives as may be agreed upon by the Parties, with an equal number of representatives designated by each of the Parties. The initial members of the JDC will be nominated by the Parties promptly following the Closing Date. Such representatives shall be individuals suitable in seniority and experience and having sufficient authority to make decisions of the JDC with respect to matters within the scope of the JDC's responsibilities. The JDC shall operate in accordance with the provisions of this Article 6, and shall have no authority to alter, amend or waive the terms and conditions of this Agreement. A Party may change one or more of its representatives serving on the JDC at any time upon written notice to the other Parties, *provided* that such replacement satisfies the requirements set forth above in this Section 6.3.1.

6.3.2 Responsibilities of JDC. The JDC shall perform the following functions:

(a) review, discuss and oversee the conduct and progress of the Parties' activities under the Development Plan and Budget, including all Clinical Trials conducted under the Development Plan and Budget;

(b) review and discuss any critical issues, including regulatory, technical or scientific issues, arising out of the conduct of the activities in the Development Plan and Budget, and provide direction on how such issues are to be resolved;

(c) review, discuss and, except for [***], revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve any proposed changes to the Development Plan and Budget, including any Additional Development Proposals and changes to the Regulatory Strategy;

(d) review, discuss and make a recommendation to the JSC regarding whether to approve any Allowable Overruns described in clause (b) of the definition thereof with respect to the Development Plan and Budget;

(e) facilitate the exchange of information regarding activities conducted under the Development Plan and Budget and the results of such activities;

(f) review and discuss the status of Development activities and regulatory activities and material communications received from Regulatory Authorities in the U.S. and the ROW Territory with respect to the Licensed Product, including in relation to the Clinical Trials and Regulatory Approval Applications for the Licensed Product; and

(g) perform such other functions as are specifically designated for the JDC in this Agreement or that the Parties mutually agree in writing to refer to the JDC.

6.3.3 JDC Meetings; Minutes.

(a) The JDC will meet in person, by videoconference or by teleconference at least once each Calendar Quarter, unless otherwise agreed by the Parties, on such dates and at such times and places as agreed to by the members of the JDC. Each Party will be responsible for its own expenses relating to attendance at, or participation in, JDC meetings. In addition to scheduled meetings, at any Party's reasonable request, the JDC may meet (including by videoconference or teleconference) upon [***] prior written notice on an ad-hoc basis to address any urgent matters that arise with respect to the Development of the Licensed Product. Each Party will ensure that its representatives at such meetings are officers or employees of such Party having sufficient seniority within the applicable Party to make decisions of the JDC with respect to matters within the scope of the JDC's responsibilities.

(b) The Alliance Managers or their designees will provide the members of the JDC with draft written minutes for approval from each meeting within [***] after each such meeting. The JDC will approve the minutes from a meeting (with each Party's representatives on the JDC collectively having one vote) within [***] after receiving such minutes. The results, reports, analyses and other information regarding the Licensed Product disclosed by one Party to the other Party through the JDC constitute Confidential Information of both Parties and may be used only in accordance with the rights granted and other terms and conditions under this Agreement. Any reports of the JDC may take the form of and be recorded in minutes of the meetings of the Parties as contemplated under this Section 6.3.3(b), including copies of any slides relating to the results and presented at such meetings.

6.4 Joint Commercialization and Medical Committee.

6.4.1 Establishment of Joint Commercialization and Medical Committee. Within [***] of the Closing Date, the Parties shall establish a joint commercialization and medical committee (the "***Joint Commercialization and Medical Committee***" or "***JCMC***") to share information between the Parties and to coordinate efforts regarding the Commercialization of, and Medical Affairs activities with respect to, the Licensed Product in the United States. The JCMC will consist of an appropriate number of representatives as may be agreed upon by the Parties, with an equal number of representatives designated by each of the Parties. The initial members of the JCMC will be nominated by the Parties promptly following the Closing Date. Such representatives shall be individuals suitable in seniority and experience and having sufficient authority to make decisions of the JCMC with respect to matters within the scope of the JCMC's responsibilities. The JCMC shall operate in accordance with the provisions of this Article 6, and shall have no authority to alter, amend or waive the terms and conditions of this Agreement. A Party may change one or more of its representatives serving on the JCMC at any time upon written notice to the other Party, *provided* that such replacement satisfies the requirements set forth above in this Section 6.4.1.

6.4.2 Responsibilities of JCMC. The JCMC shall perform the following functions:

(a) review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve the U.S. Commercialization Plan and Budget (including, for clarity, the Interim U.S. Commercialization Plan and Budget) and any proposed changes thereto;

(b) review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve the U.S. Medical Affairs Plan and Budget (including, for clarity, the Interim U.S. Medical Affairs Plan and Budget) and any proposed changes thereto;

(c) review, discuss and make a recommendation to the JSC regarding whether to approve any Allowable Overruns described in clause (b) of the definition thereof with respect to the U.S. Commercialization Plan and Budget and U.S. Medical Affairs Plan and Budget;

(d) review and oversee the conduct and progress of the Parties' activities under the U.S. Commercialization Plan and Budget and the U.S. Medical Affairs Plan and Budget;

(e) review any critical issues arising out of the conduct of the activities in the U.S. Commercialization Plan and Budget and the U.S. Medical Affairs Plan and Budget, and provide direction to the Parties on how such issue is to be resolved;

(f) facilitate the exchange of information regarding activities conducted under the U.S. Commercialization Plan and Budget and the U.S. Medical Affairs Plan and Budget and the results of such activities;

(g) discuss how to leverage the relationships each Party has with HCPs and patient communities in order to more effectively Commercialize the Licensed Products under the U.S. Commercialization Plan and Budget;

(h) review and discuss the ROW Commercialization Plan; and

(i) perform such other functions as are specifically designated for the JCMC in this Agreement or that the Parties mutually agree in writing to refer to the JCMC.

6.4.3 JCMC Meetings; Minutes.

(a) The JCMC will meet in person, videoconference or by teleconference at least once each Calendar Quarter, unless otherwise agreed by the Parties, on such dates and at such times and places as agreed to by the members of the JCMC. Each Party will be responsible for its own expenses relating to attendance at, or participation in, JCMC meetings.

(b) The Alliance Managers or their designees will provide the members of the JCMC with draft written minutes for approval from each meeting within [***] after each such meeting. The JCMC will approve the minutes from a meeting (with each Party's representatives on the JCMC collectively having one vote) within [***] after receiving such minutes. The results, reports, analyses and other information regarding the Licensed Product disclosed by one Party to the other Party through the JCMC constitute Confidential Information of both Parties and may be used only in accordance with the rights granted and other terms and conditions under this Agreement. Any reports of the JCMC may take the form of and be recorded in minutes of the meetings of the Parties as contemplated under this Section 6.4.3(b), including copies of any slides relating to the results and presented at such meetings.

6.5 Regulatory Working Group.

6.5.1 Establishment of Regulatory Working Group. Within [***] of the Closing Date, the Parties shall establish a regulatory working group (the "***Regulatory Working Group***" or "***RWG***") as a working group of the JDC. The RWG will consist of an appropriate number of representatives as may be agreed upon by the Parties, with an equal number of representatives designated by each of the Parties. The initial members of the RWG will be nominated by the Parties promptly following the Closing Date. Such representatives shall be individuals suitable in seniority and experience and having sufficient authority to make decisions of the RWG with respect to matters within the scope of the RWG's responsibilities. The RWG shall operate in accordance with policies and procedures that to be agreed by the RWG, and shall have no authority to alter, amend or waive the terms and conditions of this Agreement. A Party may change one or more of its representatives serving on the RWG at any time upon written notice to the other Party, *provided* that such replacement satisfies the requirements set forth above in this Section 6.5.1.

6.5.2 **Responsibilities of RWG**. The RWG shall perform the following functions:

(a) develop a Regulatory Strategy and any updates thereto for the JDC to review, discuss, revise (if and as appropriate) and make a recommendation to the JSC regarding whether to approve;

(b) further define (in a manner that is consistent with Article 4) the regulatory roles and responsibilities of each Party;

(c) define the access and transfer methods (such as secure databases) through which the Parties would share draft communications and Regulatory Filings and other data and information required or reasonably requested to obtain and maintain Regulatory Approvals consistent with Article 4; and

(d) review, discuss and determine [***] certain regulatory communications and Regulatory Filings made by Akcea in accordance with Article 4.

6.6 **Decision-Making**.

6.6.1 **General Decision-Making Process**. Each Party's representatives on the JSC and each Subcommittee will, collectively, have one vote (the "***Party Vote***") on all matters brought before such committee for a decision by consensus. The JSC and each Subcommittee will make decisions as to matters within its jurisdiction by unanimous Party Vote, which will be reflected in the minutes of the committee meeting. Except as otherwise expressly set forth in this Agreement, the words "determine" or "approve" by the JSC or any Subcommittee and similar phrases used in this Agreement will mean approval in accordance with this Section 6.6. For the avoidance of doubt, matters that are specified in Section 6.1.2, Section 6.3.2, Section 6.4.2 or Section 6.5.2, to be reviewed and discussed (as opposed to approved) do not require any agreement by the JSC or any Subcommittee and are not subject to the voting and decision-making procedures set forth in this Section 6.6.

6.6.2 **Decisions of the Subcommittees**. If any Subcommittee cannot reach unanimous agreement using good faith efforts on any matter within its respective scope of authority within [***], or such shorter time as may be determined by the Parties, after it begins discussing any such matter, then a Party, through its Alliance Manager, may refer such matter to the JSC for resolution in accordance with Section 6.6.3.

6.6.3 **Decisions of the JSC**. The JSC will use good faith efforts, in compliance with this Section 6.6.3, to promptly resolve any such matter for which it has authority. If, after the use of good faith efforts, the JSC is unable to resolve any such matter referred to it by any Subcommittee or any other matter within the scope of the JSC's authority, in each case, within [***], or such shorter time as may be determined by the Parties, after the matter was escalated to or discussed at a meeting by the JSC, then a Party may refer such matter to the Parties' respective Senior Officers for resolution in accordance with Section 6.6.4.

6.6.4 **Referral to Senior Officers**. If a Party makes an election under Section 6.6.3 to escalate for resolution by the Senior Officers a matter as to which the JSC cannot reach a consensus decision, then the Senior Officers will use good faith efforts to resolve any such matter so escalated to them as soon as practicable but in any event within [***] after such matter is escalated to them, and any final decision that the Senior Officers agree to in writing will be conclusive and binding on the Parties.

6.6.5 **Final Decision-Making Authority**. If the Senior Officers are unable to reach agreement on any such matter so referred within [***] after such matter is referred to them (or such longer period as the Senior Officers may agree upon), then:

(a) except as set forth in Section 6.6.5(c) and subject to Section 3.6.2(a)(i), with respect to updates or changes to the Development Plan and Budget (other than updates or amendments for ROW Development Activities that would not be reasonably expected to impact the U.S. Development Activities), any updates or changes require mutual agreement of the Parties (and, absent such agreement, the *status quo* remains except as set forth in Section 2.5);

(b) with respect to updates or changes to the ROW Development Activities that would not be reasonably expected to impact the U.S. Development Activities, AstraZeneca has final decision-making authority (and otherwise, such matter shall require mutual agreement of the Parties);

(c) with respect to the Regulatory Strategy, [***] has final decision-making authority;

(d) with respect to any Regulatory Filing or communication made by Akcea, [***] has final decision-making authority, except to the extent such Regulatory Filing or communication implicates [***], in which case [***] has final decision-making authority to the extent of such matters (*provided* such Regulatory Filing or communication is consistent with the Regulatory Strategy);

(e) with respect to the U.S. Commercialization Plan and Budget or any updates or amendments thereto, subject to Section 3.2.1 and Section 3.2.3(b), [***] has final decision-making authority (*provided* that [***] cannot exercise its final decision making authority in a manner that requires [***] to perform any Co-Commercialization and Medical Affairs Activities without [***] consent);

(f) with respect to the U.S. Medical Affairs Plan and Budget or any updates or amendments thereto, subject to Section 3.2.2, [***] has final decision-making authority (*provided* that [***] cannot exercise its final decision making authority in a manner that causes [***] to perform any Co-Commercialization and Medical Affairs Activities without [***] consent);

(g) with respect to any disputed amount included in a cost notice pursuant to Section 2.4.1(b)(i), Section 2.4.1(b)(ii), Section 3.4.1(b)(i) or Section 11.10.2, no Party shall have final decision-making authority and instead, such matter will be subject to resolution in accordance with Section 17.1.2; and

(h) with respect to the approval of any amount, on an activity-by-activity basis, that is [***] or more than the most recent JSC-approved budgeted costs and expenses for the applicable activity for a Calendar Year on a year-to-date basis set forth in any Development Plan and Budget, U.S. Medical Affairs Plan and Budget, or U.S. Commercialization Plan and Budget, as applicable, as an Allowable Overrun, such decision will require mutual agreement of the Parties.

For purposes of this Agreement, decisions of the JSC in accordance with Section 6.6.3, decisions of the Senior Officers in accordance with Section 6.6.4, and exercise by a Party of its final decision making authority in accordance with Section 6.6.5, in each case, will be considered a decision of the Subcommittee or JSC, as applicable, in which the matter was first subject to a decision.

6.6.6 Limitation on Decision-Making. Notwithstanding anything to the contrary set forth in this Agreement, without the other Party's prior written consent, neither Party (in the exercise of a Party's final decision-making authority), nor the JSC nor any Subcommittee thereof, may make a decision that could reasonably be expected to: (a) require a Party to take any action that such Party reasonably believes would (i) violate any applicable Law, the requirements of any Regulatory Authority, or any agreement with any Third Party entered into by such Party or (ii) require such Party to infringe or misappropriate any intellectual property rights of any Third Party; or (b) conflict with, amend, interpret, modify, or waive compliance by a Party under, this Agreement.

6.7 Discontinuation.

6.7.1 Subject to Section 17.11, the JSC shall continue to exist until the earliest of (a) the Parties mutually agreeing in writing to disband the JSC, (b) written notice from Akcea that it desires to disband the JSC, and (c) the end of the Royalty Term in the U.S.

6.7.2 The JDC shall continue to exist until the earliest of (a) the JSC disbanding, (b) completion of activities under the Development Plan and Budget, and (c) the Parties mutually agreeing in writing to disband the JDC.

6.7.3 The JCMC shall continue to exist until the earliest of (a) the JSC disbanding, (b) the date on which the Parties cease all Co-Commercialization and Medical Affairs Activities of the Licensed Product in the U.S., (c) the Opt-Out Date and (d) the Parties mutually agreeing in writing to disband the JCMC.

6.7.4 The RWG shall continue to exist until the earliest of (a) the JSC disbanding, (b) the JDC disbanding, and (c) the Parties mutually agreeing in writing to disband the RWG.

6.7.5 Notwithstanding anything herein to the contrary, once the JSC, JDC, JCMC or Regulatory Working Group disbands in accordance with this Agreement, such committee or working group shall be terminated and shall have no further rights or obligations under this Agreement, and thereafter any requirement of Akcea to provide information or other materials to such committee or working group shall be deemed a requirement to provide such information or other materials to AstraZeneca, AstraZeneca shall have the right to solely decide, without consultation with Akcea, all matters subject to the review or approval by such committee or working group hereunder that were previously subject to AstraZeneca's final decision-making authority and all other matters subject to the review or approval by such committee or working group hereunder will be decided by mutual agreement of the Parties.

6.8 **Alliance Managers**. Each Party will appoint a representative to act as its alliance manager (each, an "***Alliance Manager***") to progress the activities under this Agreement. The role of the Alliance Manager is to act as a single point of contact between the Parties to assure a successful collaboration. The Alliance Managers shall attend all meetings of the JSC, JDC, and JCMC (and each Alliance Manager may attend any other committee or working group meetings he or she desires to attend) as non-voting participants and support the committee or working group in the discharge their responsibilities. Alliance Managers may not serve as a member of any committee or working group but shall be non-voting participants in committee or working group meetings. An Alliance Manager may bring any matter to the attention of any committee or working group if such Alliance Manager reasonably believes that such matter warrants such attention. Each Alliance Manager will be responsible for performing the activities listed in Schedule 6.8. Each Party may change its Alliance Manager at any time upon written notice to the other Party.

6.9 **Annual Review**. Without limiting the other provisions of this Article 6, on at least an annual basis during the Term, senior leaders of each Party will meet at a mutually agreed time and place, which may include by videoconference or teleconference, to discuss the progress of the Development, Manufacturing, Commercialization and other Exploitation of the Licensed Product under this Agreement and any issues arising with respect thereto or otherwise with respect to the relationship of the Parties.

ARTICLE 7
GENERAL PROVISIONS RELATING TO THE PROGRAM

7.1 **Compliance**. Each Party and its Affiliates will perform its activities pursuant to this Agreement (and will use Commercially Reasonable Efforts to require any applicable Third Parties to perform any such activities) in compliance with all applicable Laws and regulations, including Good Laboratory Practices (cGLP), Good Clinical Practices (cGCP), and Good Manufacturing Practices (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 or which are otherwise affected.

7.2 Subcontracting Rights.

7.2.1 AstraZeneca Subcontractors. Subject to the terms and conditions of this Agreement, including Section 7.2.3, AstraZeneca will have the right to engage Affiliates or Third Party subcontractors to perform any of its obligations under this Agreement at its sole discretion; *provided* that [***].

7.2.2 Akcea Subcontractors. Subject to the terms and conditions of this Agreement, including Section 7.2.3, Akcea will have the right to engage Affiliates or Third Party subcontractors to perform its obligations under the Development Plan and Budget, the Manufacturing Transition Plan, the U.S. Commercialization Plan and Budget and U.S. Medical Affairs Plan and Budget, at its sole discretion; *provided* that [***] (Existing Third Party Subcontractors); *provided, further,* that, [***], in which case [***] under the Development Plan and Budget, the Manufacturing Transition Plan, the U.S. Commercialization Plan and Budget or the U.S. Medical Affairs Plan and Budget [***].

7.2.3 Subcontract Requirements. Any Affiliate or Third Party subcontractor to be engaged by a Party to perform a Party's obligations set forth in this Agreement will meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity; *provided* that any Party engaging an Affiliate or Third Party subcontractor hereunder will remain principally responsible and obligated for such activities and for such Affiliate or Third Party's compliance with all applicable terms and conditions of this Agreement. Notwithstanding anything to the contrary in this Agreement, the Parties may only engage a Third Party subcontractor to perform its activities under the Agreement if: (a) no rights of the other Party under this Agreement would be diminished or otherwise adversely affected as a result of such subcontracting, (b) the subcontractor undertakes the obligations of confidentiality and non-use regarding Confidential Information that are substantially the same as those undertaken by the Parties pursuant to Article 13 hereof, and (c) the subcontractor agrees that any intellectual property developed in the course of the work hereunder, other than improvements to such subcontractor's background intellectual property, shall be assigned or exclusively and perpetually licensed to such subcontracting Party to the extent required to permit licensing of such intellectual property to the other Party as required by the terms and conditions of this Agreement.

7.3 Materials Transfer. In order 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 pursuant to a Materials Transfer Agreement to be agreed and executed by the Parties. 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 and the Materials Transfer 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 the Materials Transfer Agreement or upon the written consent of the supplying Party. The receiving Party shall not use, or authorize use of, the provided materials on or in humans for any purpose under any circumstances, unless specifically provided in the Development Plan and Budget or the Materials Transfer Agreement. The receiving Party acknowledges that the provided materials are experimental in nature and may have unknown characteristics and therefore agrees to use prudence and reasonable care in the use, handling, storage, transportation and disposition and containment of such materials. ANY SUCH MATERIALS ARE SUPPLIED TO THE OTHER PARTY "AS IS", WITH NO WARRANTIES, EXPRESS OR IMPLIED, AND THE PROVIDING PARTY EXPRESSLY DISCLAIMS ANY WARRANTY OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF ANY THIRD PARTY. For clarity, this Section 7.3 shall not apply to the supply of any Licensed Compound, analytical reagents, raw materials, drug substance or drug product supplied or transferred pursuant to Article 5.

ARTICLE 8
LICENSE GRANTS

8.1 License Grant to AstraZeneca.

8.1.1 Subject to the terms and conditions of this Agreement and effective as of the Closing Date, Akcea hereby grants to AstraZeneca, and AstraZeneca accepts, an exclusive (even as to Akcea and its Affiliates), royalty-bearing, non-transferable (except in accordance with Section 17.3), sublicensable (through multiple tiers, but subject to Section 8.3) license under the Licensed Technology to Exploit the Licensed Compounds and the Licensed Products in the Field in the Territory; *provided* that (a) [***] and (b) for clarity, the license grant under this Section 8.1 shall not include the right to Exploit the Licensed Compounds and the Licensed Products in the PTC Territory unless and until the date that is the earlier of (i) such time as Akcea shall have the right to grant the foregoing exclusive license to AstraZeneca in the PTC Territory pursuant to Sections 7.1 and 7.2 of the PTC Agreement and (ii) such time as Akcea and its Affiliates are otherwise no longer subject to Sections 7.1 and 7.2 of the PTC Agreement (such date, the "***PTC Territory License Date***") (*provided* that, if any antitrust approvals are required under applicable Law in any country in the PTC Territory prior to the inclusion of rights for AstraZeneca in such country under this Agreement, then the Parties will cooperate in good faith in accordance with Section 10.2 (*mutatis mutandis* with respect to such country) to promptly secure such approvals, and the PTC Territory License Date shall be the date that all such approvals are received). If Akcea or any of its Affiliates [***], then Akcea will (1) [***], (2) [***], and (3) [***].

8.1.2 Subject to the terms and conditions of this Agreement and effective as of the Closing Date, Akcea hereby grants to AstraZeneca, and AstraZeneca accepts, a non-exclusive, royalty-bearing, non-transferable (except in accordance with Section 17.3), sublicensable (through multiple tiers, but subject to Section 8.3) license under the Licensed Technology to Manufacture and Develop Licensed Compounds and Licensed Products in the [***] solely for the purpose of Developing and Commercializing Licensed Compounds and Licensed Products [***].

8.2 License Grants to Akcea.

8.2.1 Subject to the terms and conditions of this Agreement and effective as of the Closing Date, AstraZeneca hereby grants to Akcea, and Akcea accepts, a non-exclusive, royalty-free, non-transferable (except in accordance with Section 17.3), sublicensable (through multiple tiers, but solely to Akcea's Affiliates and its and their subcontractors permitted under Section 7.2.2) (sub)license under the Licensed Technology and the AstraZeneca IP to (a) perform U.S. Development Activities and Global Development Activities in the Field in the Territory pursuant to the Development Plan and Budget (to the extent permitted under Article 2) and (b) Manufacture (to the extent permitted under Article 5) the Licensed Compound and the Licensed Product in the Field in the Territory through the later of (i) [***] and (ii) [***].

8.2.2 Subject to the terms and conditions of this Agreement and effective as of the Closing Date, AstraZeneca hereby grants to Akcea, and Akcea accepts, a non-exclusive, royalty-free, non-transferable (except in accordance with Section 17.3), sublicensable (through multiple tiers, but solely to Akcea's Affiliates and its and their subcontractors permitted under Section 7.2.2) (sub)license under the Licensed Technology and the AstraZeneca IP to perform Co-Commercialization and Medical Affairs Activities (to the extent permitted under Article 3) for the Licensed Compound and the Licensed Product in the Field in the United States.

8.3 **AstraZeneca's Sublicensing Rights**. Subject to the terms and conditions of this Agreement, AstraZeneca will have the right to grant sublicenses under the licenses granted under Section 8.1 above:

8.3.1 under the Licensed Technology other than Akcea Manufacturing IP to an Affiliate of AstraZeneca or a Third Party; *provided* that Akcea's prior written consent (not to be unreasonably withheld, conditioned, or delayed) will be required for any sublicense to a Third Party of Commercialization rights in the U.S. (except any sublicense to a CSO or other vendor or service provider); and

8.3.2 under the Akcea Manufacturing IP solely to (a) [***], (b) [***] (each, an "***Authorized CMO***"), which such Authorized CMOs as of the Execution Date are set forth on Schedule 8.3.2 attached hereto, or (c) [***].

8.4 **Sublicense Conditions**. For each such sublicense granted by AstraZeneca under its licenses set forth in Section 8.1 (other than a Settlement Sublicense) or Akcea under its licenses set forth in Section 8.2 (a "***Sublicense***"), the sublicensing Party shall promptly notify the other Party of the granting of such Sublicense, and shall ensure that the terms of such Sublicense (a) are subject to the applicable terms and conditions of this Agreement and (b) without limiting the foregoing, contain provisions requiring that the Sublicensee (i) undertakes the obligations of confidentiality and non-use regarding Confidential Information that are substantially the same as those undertaken by the Parties pursuant to Article 13 hereof, (ii) agrees that any intellectual property developed in the course of the work hereunder shall be assigned or licensed to the sublicensing Party to the extent required to permit licensing of such intellectual property to the other Party as required by the terms and conditions of this Agreement, and (iii) submits applicable sales or other reports to the sublicensing Party to the extent necessary or relevant to the reports or records required to be maintained under this Agreement. The sublicensing Party will provide the other Party with a fully-executed copy of any agreement reflecting any such Sublicense (excluding any Sublicense with an Affiliate of the sublicensing Party), which may be reasonably redacted to exclude the sublicensing Party's proprietary information, other competitively sensitive information, or any other information not necessary for the other Party to verify compliance with the preceding sentence, promptly (but no later than [***]) after the execution thereof, which copy shall be treated as the sublicensing Party's Confidential Information. The sublicensing Party assumes full responsibility, and will remain primarily liable, for causing the performance of all obligations of each of its Sublicensees/(sub)licensees and their compliance with all applicable terms and conditions of this Agreement.

8.5 **Effect of Termination on Sublicenses**. If this Agreement terminates for any reason, any Sublicensee will, from the effective date of such termination, automatically become a direct licensee of Akcea with respect to the rights sublicensed to the Sublicensee by AstraZeneca; *so long as* (a) such Sublicensee is not in breach of its Sublicense, (b) Akcea is not required to assume any obligations or liabilities (contingent or otherwise) not set forth in this Agreement, (c) such Sublicensee agrees in writing to comply with all of the terms and conditions of this Agreement to the extent applicable to the rights originally sublicensed to it by AstraZeneca, and (d) such Sublicensee agrees to pay directly to Akcea AstraZeneca's payments under this Agreement to the extent applicable to the rights sublicensed to it by AstraZeneca.

8.6 **Technology Transfer**. After the Closing Date, Akcea will promptly deliver copies of the Know-How licensed to AstraZeneca under Section 8.1 (other than the Akcea Manufacturing and Analytical Know-How which will be transferred pursuant to Section 5.2) in Akcea's possession or control that has not previously been provided hereunder, for use solely in accordance with the license granted under Section 8.1. To assist with the transfer of such Know-How and if reasonably requested by AstraZeneca, Akcea will make its personnel reasonably available to AstraZeneca during normal business hours to transfer such Know-How under this Section 8.6. Any Out-of-Pocket Costs incurred by either Party in connection with this transfer will be considered Other Operating Expenses and shared by the Parties in accordance with Section 11.10. Without limiting the foregoing, upon Completion of each Clinical Trial ongoing as of the Execution Date, Akcea will, as soon as reasonably practicable, transfer to AstraZeneca the clinical and regulatory databases with respect to such Clinical Trial.

8.7 **Consequence of Natural Expiration of this Agreement**. If this Agreement expires (*i.e.*, is not terminated early) in a particular country in accordance with Section 16.1 then the license granted to AstraZeneca under the Licensed Technology shall become perpetual, irrevocable and fully paid-up on a country-by-country basis.

8.8 **No Other Rights and Retained Rights**. Except as otherwise expressly provided in this Agreement, under no circumstances will a Party, as a result of this Agreement, obtain any ownership interest, license right or other right in any Know-How, Patent Rights or other intellectual property rights of the other Party or any of its Affiliates, including items owned, controlled, developed or acquired by the other Party or any of its Affiliates, or provided by the other Party to the first Party at any time pursuant to this Agreement. AstraZeneca will not practice the Licensed Technology other than as expressly licensed and permitted under this Agreement, and Akcea will not practice the AstraZeneca IP other than as expressly licensed and permitted under this Agreement. Any rights not expressly granted to a Party by the other Party under this Agreement are hereby retained by such other Party.

8.9 **Section 365(n) of the Bankruptcy Code**. The Parties intend to take advantage of the protections of Section 365(n) (or any successor provision) of the U.S. Bankruptcy Code or any analogous provisions in any other country or jurisdiction to the maximum extent permitted by Law. All rights and licenses granted under or pursuant to this Agreement by a Party to the other Party, but only to the extent they constitute licenses of a right to "intellectual property" as defined in Section 101 of the U.S. Bankruptcy Code or foreign counterparty thereto, are and will otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code or any foreign counterpart thereto, licenses of rights to "*intellectual property.*" The Parties agree that the Parties will retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code and any foreign counterpart thereto, including the right to obtain the intellectual property from another entity. In the event of the commencement of a bankruptcy proceeding by or against either Party under the U.S. Bankruptcy Code or any foreign counterparty thereto, the Party that is not subject to such proceeding will further be entitled to a complete duplicate of, or complete access to, any such intellectual property, and all embodiments which, if not already in its possession, will be promptly delivered to the non-subject Party upon written request (a) upon commencement of a bankruptcy proceeding, unless the Party subject to such proceeding continues to perform all of its obligations under this Agreement, or (b) if not delivered pursuant to clause (a) above because the subject Party continues to perform, upon the rejection of this Agreement by or on behalf of the subject Party. Unless and until the subject Party rejects this Agreement, the subject Party shall perform this Agreement or provide the intellectual property (including all embodiments of such intellectual property) to the non-subject Party, and shall not interfere with the rights of the non-subject Party to such intellectual property, including the right to obtain the intellectual property from another entity. The upfront fee, milestone payments and Royalties to be paid by AstraZeneca under this Agreement will be considered "*royalties*" for purposes of Section 365(n) of the U.S. Bankruptcy Code.

8.10 **License Conditions; Limitations**. The licenses granted under Section 8.1 and the sublicense rights under Section 8.3 are subject to and limited by (a) the Prior Agreements, (b) the Existing In-License Agreements (in each case of clauses (a) and (b), to the extent and in the form that such agreements are disclosed to AstraZeneca as of the Execution Date or as such agreements may be amended as permitted by this Agreement), (c) subject to Akcea's compliance with Section 11.8.4, any Future In-License Agreements (in the case of this clause (c), to the extent and in the form that such agreements (and any amendments thereto) are disclosed to AstraZeneca pursuant to the terms of Section 14.4.8 and as such agreements may be amended as permitted by this Agreement) and (d) the granting of, or performance of obligations under, Permitted Licenses.

ARTICLE 9
ROFN AND EXCLUSIVITY PROVISIONS

9.1 **ROFN for [***]**. During the Exclusivity Period, if Akcea or any of its Affiliates discovers or otherwise obtains rights to a [***] and intends to [***] (itself or through a Third Party) (such Development program, "***Potential*** [***]"), then Akcea shall provide prompt notice to AstraZeneca in writing (each such written notice, a "***Notice of Intent***"), which Notice of Intent will include a detailed description of such Potential [***]. Following a Notice of Intent, Akcea shall promptly provide AstraZeneca with other information and documentation reasonably related to such Potential [***] that is requested by AstraZeneca within [***] after AstraZeneca's receipt of the Notice of Intent. AstraZeneca shall have [***] from the later of receipt of the Notice of Intent or receipt of any information or documentation related to such Potential [***] that is reasonably requested by AstraZeneca within [***] of receipt of the Notice of Intent within which to inform Akcea in writing that AstraZeneca has an interest in obtaining exclusive Development and Commercialization rights from Akcea with respect to such [***] (each such written notice, a "***Statement of Interest***"). Following receipt of a timely Statement of Interest, Akcea will negotiate in good faith exclusively with AstraZeneca for [***] (or such longer period mutually agreed to by the Parties, the "***Negotiation Period***") the financial and other material terms and conditions of this Agreement that the Parties would amend in consideration for including the Potential [***] as part of this Agreement (the "***Right of First Negotiation***"). Subject to the foregoing, during the applicable Negotiation Period, [***]. If AstraZeneca does not provide a Statement of Interest within the [***] period, or if AstraZeneca does provide a Statement of Interest but the Parties do not reach agreement regarding the terms of such a transaction within the Negotiation Period, then such Right of First Negotiation with respect to such Potential [***] shall expire, and Akcea will have the right to progress the Development of such Potential [***], subject to the remainder of this Article 9; *provided* that [***]. Any agreement reached by the Parties with respect to the Potential [***] shall be memorialized in and governed by an amendment to this Agreement or a separate written agreement addressing the terms and conditions of such Potential [***].

9.2 **Exclusivity Covenants**. Except in the performance of its obligations or exercise of its rights under this Agreement and except as otherwise set forth in Section 9.3 and Section 9.4, for the period commencing on the Closing Date and expiring upon the earlier of (a) [***], and (b) [***] (the "***Exclusivity Period***"), neither Party nor any of its respective Affiliates will, either alone or with or for any Third Party, work independently or for or with any Third Party (including the grant of any license or other rights to any Third Party) with respect to the Development or Commercialization of a Competitive Oligo. Notwithstanding anything to the contrary in this Agreement and solely for purposes of this Section 9.2 and Section 9.4, "*Development*" will be deemed to exclude all pre-clinical research and pre-clinical development activities, such that pre-clinical research and pre-clinical development activities will not violate this Section 9.2.

9.3 **Limitations and Exceptions to Akcea's Exclusivity Covenants**. Akcea's or its Affiliates' practice of the following will not violate Section 9.2:

9.3.1 the licenses granted by Akcea or its Affiliates, or the performance by Akcea or its Affiliates of any obligations, under the Prior Agreements;

9.3.2 the granting of, or performance of obligations under, Permitted Licenses;

9.3.3 any activities permitted under Section 9.4 below;

9.3.4 the Exploitation of any Inotersen Product; and

9.3.5 [***].

9.4 **Competitive Oligo Transactions**.

9.4.1 The Parties acknowledge that after the Execution Date a Party or its Affiliate may acquire a Third Party (including through merger, reorganization, consolidation or business combination). In the case of such a transaction after the Execution Date and prior to the end of the Exclusivity Period where such Third Party is Developing or Commercializing a Competitive Oligo that would violate Section 9.2, notwithstanding anything to the contrary in this Agreement, within [***] after such acquisition (or if at the time of such acquisition there are ongoing Clinical Trials, if later, within [***] after Completion of such Clinical Trials), such Party (or its Affiliate) and such Third Party must either (a) [***], (b) [***], (c) [***], or (d) [***]. If such acquiring Party (or its Affiliate) and such Third Party do not take one of the steps set forth in clause (a) through clause (d) above (as applicable) or do not comply with the immediately following sentence, then such Development or Commercialization of such Competitive Oligo will be a violation of Section 9.2. During the period between the closing of such acquisition and the date that the acquiring Party (or its Affiliate) completes one of the steps set forth in clause (a) through clause (d) above, the acquiring Party shall establish reasonable procedures, including firewalls between the teams responsible for such Competitive Oligo and the teams responsible for the Licensed Product (other than members of senior management of the acquiring Party responsible for overall product portfolio management), to prevent the use of any Confidential Information of the other Party or any Patent Rights or Know-How that are subject to a license grant under this Agreement from being used by the acquiring Party or its Affiliates in connection with the Development or Commercialization of such Competitive Oligo.

9.4.2 The Parties acknowledge that after the Execution Date a Party may undergo a Change of Control (including through merger, reorganization, consolidation or business combination). In the case of a Change of Control after the Execution Date and prior to the end of the Exclusivity Period where the Acquirer or its pre-existing Affiliate (other than a Party Affiliate) is, at the time of such Change of Control, Developing or Commercializing a Competitive Oligo that would violate Section 9.2 if conducted by a Party or its Affiliate, the continued Development or Commercialization of such Competitive Oligo will not be a violation of Section 9.2, *provided* that the Acquirer establishes reasonable procedures, including firewalls between the teams responsible for such Competitive Oligo and the teams responsible for the Licensed Product (other than members of senior management of the Acquirer responsible for overall product portfolio management), to prevent the use of any Confidential Information of the other Party or any Patent Rights or Know-How that are subject to a license grant under this Agreement from being used by the Acquirer or its Affiliates in connection with the Development or Commercialization of such Competitive Oligo.

ARTICLE 10
CLOSING

10.1 **Closing**. Subject to the last sentence of Section 16.1, the closing of the transactions contemplated by this Agreement (the "***Closing***") shall be deemed to have taken place on the date that all necessary authorizations, consents, orders or approval of, or declarations or filings with, or expirations of waiting periods under the HSR Act, as applicable to the consummation of the transactions contemplated by this Agreement ("***HSR Clearance***") have been received, authorized, permitted or expired (the "***Closing Date***"). AstraZeneca shall immediately provide written notice to Akcea of such Closing Date. Except for the Parties' rights and obligations under Section 2.3 (Development Activities Prior to Closing Date), Article 13 (Confidentiality), Article 14 (Representations and Warranties), Section 17.1 (Dispute Resolution), Section 17.2 (Governing Law; Jurisdiction; Equitable Relief; Losses; Remedies), Section 17.11 (Change of Control) and this Article 10 (Closing), which will be effective as of the Execution Date, this Agreement will not become effective until the Closing Date. Upon the occurrence of the Closing Date, all other provisions of this Agreement shall become effective automatically without the need for further action by the Parties.

10.2 **Antitrust Filings**.

10.2.1 Akcea and AstraZeneca shall, as promptly as practicable (but no later than 10 Business Days after the Execution Date), and before the expiration of any relevant legal deadline, prepare and file with the United States Federal Trade Commission and the Antitrust Division of the United States Department of Justice, the Notification and Report Form for Certain Mergers and Acquisitions (as that term is defined in the HSR Act) required for the transactions contemplated hereby, together with all required documentary attachments thereto any supplemental information requested in connection therewith pursuant to the HSR Act (the "***Antitrust Filings***"). Notwithstanding the foregoing, the Parties may, upon mutual agreement, delay the filing of any of the Antitrust Filings if they reasonably believe that such delay would result in obtaining any clearance required under the HSR Act for the consummation of this Agreement and the transactions contemplated hereby more expeditiously. Each of Akcea and AstraZeneca shall cooperate in the antitrust clearance process, including by furnishing to each other's counsel such necessary information and reasonable assistance as the other may request in connection with its preparation of any filing or submission that is necessary under the HSR Act and to furnish promptly with the Antitrust Authorities any information reasonably requested by them in connection with such filings. Each Party shall be responsible for its own fees, costs and expenses associated with any Antitrust Filings or in connection with its obligations pursuant to this Section 10.2.

10.2.2 Akcea and AstraZeneca shall use their commercially reasonable efforts to promptly obtain HSR Clearance and shall keep each other apprised of the status of any communications with, and any inquiries or requests for additional information from, any Antitrust Authority and shall comply promptly with any such inquiry or request. Commercially reasonable efforts as used in this Section 10.2.2 will not include proposing, negotiating, committing to or effecting, by consent decree, hold separate order, or otherwise, (a) the sale, divestiture, disposition, licensing or sublicensing of any of a Party's or its Affiliates' assets, properties or businesses, (b) behavioral limitations, conduct restrictions or commitments with respect to such assets, properties or business, or of any of the rights or obligations of a Party under this Agreement, or (c) defending through litigation any claim asserted in court by any Third Party that would restrain, prevent or delay the Closing Date.

10.2.3 Subject to Section 10.2.2, the Parties shall instruct their respective counsel to cooperate with each other and use commercially reasonable efforts to facilitate and expedite the identification and resolution of any issues arising under the HSR Act at the earliest practicable dates. Such commercially reasonable efforts and cooperation include counsel's undertaking (a) to keep each other informed of communications, inquiries and requests from and to personnel of the reviewing Antitrust Authorities, including by providing copies thereof to the other Party (subject to reasonable redactions for privilege or confidentiality concerns), and (b) to confer with each other regarding appropriate contacts with and response to personnel of such Antitrust Authorities and the content of any such contacts or presentations. Each of Akcea and AstraZeneca shall consult with the other Party, to the extent practicable, in advance of participating in any substantive meeting or discussion with any Antitrust Authority with respect to any such filings, applications, investigation, or other inquiry and, to the extent permitted by the relevant Antitrust Authority, give the other Party the opportunity to attend and participate in such meeting or discussion (which, at the request of either AstraZeneca or Akcea, shall be limited to outside antitrust counsel only). Akcea and AstraZeneca shall each give the other Party the opportunity to review in advance, and shall consider in good faith the other Party's reasonable comments in connection with, the content of any presentations, white papers or other written materials to be submitted to any Antitrust Authority. Neither Party shall withdraw its filing under the HSR Act or agree to delay the Closing Date without the prior written consent of the other Party. The Parties' rights and obligations hereunder apply only in so far as they relate to this Agreement and to the transactions contemplated under this Agreement.

10.3 **Covenants between Signing and Closing**. From the Execution Date and until the Closing Date or the earlier termination of this Agreement in accordance with Article 16, except as consented to in writing by AstraZeneca, (a) Akcea shall conduct its business with respect to the Licensed Product in the ordinary course of business consistent with past practice and in accordance with all applicable Law with respect to the performance of its obligations under this Agreement, including with respect to its activities under any Clinical Trials of the Licensed Product that are ongoing as of the Execution Date, and (b) Akcea shall not (i) license, transfer or otherwise dispose of any Licensed Technology; (ii) abandon, cancel or allow to lapse or fail to maintain or protect any Licensed Technology; or (iii) enter into, modify, extend, renew or amend any contract, in each case of (i), (ii) and (iii) that would materially limit or impair Akcea's or its Affiliates' ability to carry out its obligations or AstraZeneca's rights under this Agreement.

ARTICLE 11
UPFRONT FEE; MILESTONES AND ROYALTIES; REIMBURSEMENTS; PAYMENTS

11.1 **Upfront Fees**.

11.1.1 **U.S. Rights**. In partial consideration for the rights and licenses granted to AstraZeneca hereunder with respect to the U.S., and subject to the terms and conditions of this Agreement, within 30 days after receipt of an invoice from Akcea, which invoice may be issued on or after the Closing Date but not earlier than December 10, 2021, AstraZeneca will pay Akcea a one-time upfront fee of $100,000,000.

11.1.2 **ROW Rights**. In partial consideration for the rights and licenses granted to AstraZeneca hereunder with respect to the ROW Territory, and subject to the terms and conditions of this Agreement, within 30 days after receipt of an invoice from Akcea, which invoice may be issued on or after the Closing Date but not earlier than December 10, 2021, AstraZeneca will pay Akcea a one-time upfront fee of $100,000,000.

11.2 **Development and Regulatory Milestone Payments**. In further consideration for the rights and licenses granted to AstraZeneca hereunder, and subject to the terms and conditions of this Agreement (including Section 11.6.2(d)), in accordance with Section 11.4, AstraZeneca will pay Akcea the one-time milestone payments set forth in TABLE 1 below when a Development or regulatory milestone event listed in TABLE 1 is first achieved by or on behalf of AstraZeneca or its Affiliates or its or their Sublicensees after the Closing Date during the Term for a Licensed Product:

Table 1		
No.	**Milestone Event**	**Milestone Payment**
1.	[***]	$[***]*
2.	[***]	$[***]*
3.	[***]	$[***]
4.	[***]	$[***]
5.	[***]	$[***]
6.	[***]	$[***]
7.	[***]	$[***]

*Notwithstanding the foregoing, Milestone Payment No. 1 will be [***] and Milestone Payment No. 2 will be [***]; *provided* that for purposes of determining if Milestone Event No. 2 is "achieved" [***]. For example, if [***] then AstraZeneca will provide Akcea with written notice of such milestone achievement within [***] and AstraZeneca will pay Akcea $[***] within [***] after receipt of such invoice.

11.3 Sales Milestone Payments. In further consideration for the rights and licenses granted to AstraZeneca hereunder, and subject to the terms and conditions of this Agreement, AstraZeneca will pay Akcea the one-time sales milestone payments set forth in Table 2 below, in accordance with Section 11.4, when a sales milestone event listed in Table 2 is first achieved by or on behalf of AstraZeneca or its Affiliates or its or their Sublicensees after the Closing Date during the Term for the Licensed Products in a given Calendar Year:

Table 2	
Sales Milestone Event	**Sales Milestone Payment**
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]
Net Sales of all Licensed Products in the Territory in a Calendar Year are greater than $[***].	$[***]

11.4 Limitations on Milestone Payments; Exceptions; Notice.

11.4.1 Each milestone payment set forth in Table 1 and Table 2 above will be paid only once upon the first achievement of the milestone event by a Licensed Product, regardless of the number of Licensed Products that achieve such milestone event or how many times a single Licensed Product achieves such milestone event, and any subsequent or repeated achievement of the same milestone event, whether by the same Licensed Product or by a Licensed Product different from the first Licensed Product used in the same milestone event, shall not result in any additional payment obligation by AstraZeneca under Section 11.2 or Section 11.3, as applicable.

11.4.2 The sales of Licensed Products arising from named patient, compassionate use, or other similar programs will not be considered for purposes of determining whether a milestone event listed in Table 1 or Table 2 has been achieved.

11.4.3 If multiple milestone events are achieved simultaneously by the same occurrence, then the milestone payments for all such milestone events will be due simultaneously. If multiple sales milestone events are achieved in the same Calendar Year, then the milestone payments for all such milestone events will be due for such Calendar Year.

11.4.4 Each time a milestone event is achieved under this Article 11, AstraZeneca will send Akcea written notice thereof (except with respect to milestone event #7 set forth in Table 1, in which case [***]) (a) with respect to Development and regulatory milestone events set forth in Table 1, within [***] following the date of achievement of such milestone event and (b) with respect to sales milestone events set forth in Table 2, within [***] following the end of the month in which such sales-based milestone events occur, and in each case ((a) and (b)), the applicable milestone payment will be due within [***] after receipt by AstraZeneca of an invoice from Akcea (except with respect to milestone event #7 set forth in Table 1, which will be due within [***] of [***]).

11.5 U.S. Royalties.

11.5.1 US. Royalty Rates. In further consideration of the licenses and other rights granted to AstraZeneca, subject to the terms and conditions of this Agreement, including Section 3.6.2 and Section 11.5.2, on a Calendar Quarter-by-Calendar Quarter basis, AstraZeneca will pay to Akcea royalties at the U.S. Royalty Rates (set forth in TABLE 3 below) ("***U.S. Royalty Rates***") on the aggregate Net Sales resulting from the sale of Licensed Products in the U.S. during each Calendar Quarter (collectively, "***U.S. Royalties***"), which U.S. Royalty Rate for a given Calendar Year will be determined [***] as follows:

TABLE 3

[***]	**U.S. Royalty Rate**
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]%
[***]	[***]

For clarity, the U.S. Royalty Rate will be determined [***]. On a Calendar Year-by-Calendar Year basis no later than [***] prior to the start of each Calendar Year, AstraZeneca will [***]. No royalties are due on Net Sales of Licensed Products arising from named patient, compassionate use and other programs providing for the delivery of Licensed Product at no cost.

11.5.2 [***]. Within [***] after the end of each Calendar Year, AstraZeneca shall (a) [***], (b) [***], and (c) [***]. If the [***] for a Calendar Year is [***]. If the [***] for a Calendar Year is [***]. In addition, within [***] after the end of each Calendar Year, AstraZeneca will provide Akcea with a good faith, non-binding estimate of the [***].

11.5.3 U.S. Royalty Reports; Payment of U.S. Royalties. Following the First Commercial Sale of any Licensed Product in the U.S., unless and until the Opt-Out Date occurs (and for the Calendar Quarter in which the Opt-Out Date occurs), AstraZeneca will furnish to Akcea a detailed written report within [***] after the end of each Calendar Quarter during a Calendar Year showing, on a Licensed Product-by-Licensed Product basis, the Net Sales of each Licensed Product in the U.S. and the U.S. Royalties payable under this Agreement with respect to such Calendar Quarter. After receipt of such written report, Akcea will submit an invoice to AstraZeneca with respect to the U.S. Royalties payable under this Agreement with respect to such Calendar Quarter. Such U.S. Royalties will be due and payable within [***] after AstraZeneca's receipt of such invoice. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for the Licensed Product is made in the U.S. and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, AstraZeneca will provide Akcea a preliminary, non-binding written report estimating the total Net Sales of, and U.S. Royalties payable to Akcea for, Licensed Products projected for such Calendar Quarter. Additionally, within [***] after the end of each Calendar Year after the First Commercial Sale of a Licensed Product in the U.S., AstraZeneca shall provide to Akcea a non-binding [***] sales forecast by Calendar Quarter, solely for Akcea's planning purposes.

11.6 ROW Royalties.

11.6.1 ROW Royalty Rates. In further consideration of the licenses and other rights granted to AstraZeneca, during the Royalty Term, subject to the terms and conditions of this Agreement (including this Article 11), AstraZeneca will pay to Akcea royalties at the ROW Territory royalty rates (set forth in TABLE 4 below) ("***ROW Royalty Rates***") on the aggregate Net Sales resulting from the sale of each Licensed Product (a) in the ROW Territory and (b) [***] ((a) and (b), "***ROW Net Sales***"), in each case ((a) and (b)), during each Calendar Year (collectively, "***ROW Royalties***"):

TABLE 4

Royalty Tier	ROW Net Sales of Licensed Products in a Calendar Year	ROW Royalty Rate
1.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year less than $[***]	[***]%
2.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year greater than or equal to $[***] but less than $[***]	[***]%
3.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year greater than or equal to $[***] but less than $[***]	[***]%
4.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year greater than or equal to $[***] but less than $[***]	[***]%
5.	For the portion of ROW Net Sales of a Licensed Product in a Calendar Year greater than or equal to $[***]	[***]%

ROW Net Sales in a Calendar Year will be calculated by [***] during the Royalty Term. Each ROW Royalty Rate set forth in TABLE 4 above shall apply only to that portion of the Net Sales of all Licensed Products in the ROW Territory during a given Calendar Year that falls within the indicated royalty tier. No ROW Royalties are due on Net Sales of Licensed Products arising from named patient, compassionate use and other programs providing for the delivery of Licensed Product at no cost. The sales of Licensed Products arising from named patient, compassionate use, or other similar programs will not be considered a First Commercial Sale for purposes of calculating the Royalty Term. ROW Royalties will be payable on a Licensed Product-by-Licensed Product and country-by-country basis during the Royalty Term for such Licensed Product in such country until the expiration of the Royalty Term for such Licensed Product in such country. [***]. AstraZeneca will provide reports and payments to Akcea consistent with Section 11.7.

Notwithstanding any provision to the contrary set forth in this Agreement, all references to the ROW Territory in this Section 11.6, Section 11.7, Section 11.8 and Section 11.9 [***].

11.6.2 Opt-Out Scenario One Royalty and ROW Royalty Deductions.

(a) **Expiration of Valid Claims and Exclusivity**. If on a country-by-country and Licensed Product-by-Licensed Product basis, (i) the last Valid Claim of the Akcea Patent Rights or Joint Patent Rights Covering [***] such Licensed Product in such country has expired, (ii) the last Valid Claim of the Akcea Patent Rights or Joint Patent Rights listed in the Orange Book and Covering such Licensed Product in such country has expired or a Generic Product is being sold in such country, and (iii) the Regulatory Exclusivity Period in such country with respect to such Licensed Product has expired or a Generic Product is being sold in such country, then the Opt-Out Scenario One Royalty Rates or the ROW Royalty Rates, as applicable, used to calculate the Opt-Out Scenario One Royalties or the ROW Royalties, as applicable, with respect to such Licensed Product in such country shall by reduced to [***]% of the Opt-Out Scenario One Royalty Rates agreed to by the Parties or the ROW Royalty Rates set forth in Table 4, as applicable.

(b) **Opt-Out Scenario One Royalties and ROW Royalties After Generic Intrusion**. If, on a country-by-country and Licensed Product-by-Licensed Product basis, at any time during the Royalty Term, Generic Intrusion occurs in a given country with respect to a Licensed Product (including in the U.S. if Akcea exercised the Opt-Out Right), then the Opt-Out Scenario One Royalty Rates or the ROW Royalty Rates, as applicable, used to calculate Opt-Out Scenario One Royalties or the ROW Royalties, as applicable, for such Licensed Product in such country shall be reduced to [***]% of the Opt-Out Scenario One Royalty Rates agreed to by the Parties or the ROW Royalty Rates set forth in Table 4, as applicable.

(c) **Compulsory Licenses**. If a Governmental Authority requires AstraZeneca or any of its Affiliates or its or their Sublicensees to grant a compulsory license to a Third Party (each, a "***Compulsory Sublicensee***") permitting such Third Party to make and sell a Licensed Product in a country, (i) such Compulsory Sublicensee will not be considered a Sublicensee for the purpose of this Agreement, and (ii) such grant will be permitted and deemed consented to by Akcea under Section 8.3. At such time as AstraZeneca or any of its Affiliates or its or their Sublicensees enters into a sublicense with a Compulsory Sublicensee, in lieu of the Opt-Out Scenario One Royalty Rates agreed to by the Parties or the ROW Royalty Rates set forth in Table 4, as applicable, the Parties will discuss, and mutually agree upon, the sharing between Akcea and AstraZeneca of the consideration received by AstraZeneca under such compulsory license, [***]; *provided* that no such sharing will occur until [***].

(d) **Stacking**. AstraZeneca shall be entitled to credit against the ROW Royalties due to Akcea under Section 11.6 and sales milestone payments due to Akcea under Section 11.3 in a given Calendar Quarter [***]% of (i) [***] due by AstraZeneca, or any of its Affiliates or its or their Sublicensees, to a Third Party (or to Akcea under Section 5.3.1(b)) for a license or other right with respect to any Patent Right, Know-How or other intellectual property [***] to Exploit a Licensed Compound or Licensed Product, including any AstraZeneca Third Party Product-Specific License, and (ii) [***], excluding, in each case ((i) and (ii)), [***] ("***Third Party Payments***"), and in each case ((i) and (ii)), [***]; *provided* that with respect to any Third Party Payments that are attributable to Akcea's breach of its representations and warranties hereunder or for judgements related to Additional Core IP, AstraZeneca shall be entitled to deduct [***]% of such Third Party Payments, excluding amounts for which Akcea has indemnified AstraZeneca pursuant to Section 15.2. Notwithstanding the foregoing, for purposes of this Section 11.6.2(d), Third Party Payments will not include, and AstraZeneca will not be entitled to credit, any amounts that are shared by the Parties as Other Operating Expenses pursuant to Section 11.8.2(b).

11.7 Royalty Reports; Payment of Royalties. Following the First Commercial Sale of any Licensed Product in any country in the ROW Territory or the U.S. if Akcea exercised the Opt-Out Right in accordance with Section 3.6, AstraZeneca will furnish to Akcea a written report within [***] after the end of each Calendar Quarter during a Calendar Year showing, on a Licensed Product-by-Licensed Product and country-by-country basis, the Net Sales of each Licensed Product in each country and the ROW Royalties and Opt-Out Scenario One Royalties payable under this Agreement with respect to such Calendar Quarter. After receipt of such written report, Akcea will submit an invoice to AstraZeneca with respect to the ROW Royalties and Opt-Out Scenario One Royalties payable under this Agreement with respect to such Calendar Quarter. Such ROW Royalties and Opt-Out Scenario One Royalties will be due and payable within [***] after AstraZeneca's receipt of such invoice. In addition, beginning with the Calendar Quarter in which the First Commercial Sale for the Licensed Product is made in the ROW Territory or the U.S. if Akcea exercised the Opt-Out Right in accordance with Section 3.6 and for each Calendar Quarter thereafter, within [***] following the end of each such Calendar Quarter, AstraZeneca will provide Akcea a preliminary, non-binding written report estimating the total Net Sales of, and ROW Royalties and Opt-Out Scenario One Royalties payable to Akcea for, Licensed Products projected for such Calendar Quarter. Additionally, during the Royalty Term, within [***] of the end of each Calendar Year, AstraZeneca shall provide to Akcea a non-binding [***] sales forecast by Calendar Quarter, solely for Akcea's planning purposes.

11.8 Third Party Licenses.

11.8.1 Notice of Third Party IP. If a Party identifies any Third Party intellectual property rights that such Party or any of its Affiliates or sublicensees deems [***] in order to Exploit a Licensed Compound or Licensed Product in the Territory, then such Party shall promptly provide written notice to the other Party identifying such Third Party intellectual property rights.

11.8.2 Product IP. AstraZeneca, its Affiliates and its and their Sublicensees shall have the sole right to obtain a license to Exploit the Licensed Compounds and Licensed Products under any Third Party intellectual property rights that are [***] to Exploit a Licensed Product or a Licensed Compound, except for any Additional Core IP (each such license, an "***AstraZeneca Third Party Product-Specific License***").

(a) Subject to Section 11.6.2(d) and Section 11.8.2(b), if AstraZeneca elects to obtain an AstraZeneca Third Party Product-Specific License, AstraZeneca, or its applicable Affiliate or Sublicensee, shall pay all amounts due under such AstraZeneca Third Party Product-Specific Licenses.

(b) Unless and until Akcea has exercised the Opt-Out Right in accordance with Section 3.6, AstraZeneca will, prior to entering into any AstraZeneca Third Party Product-Specific License with respect to the U.S., provide notice to the JSC of any AstraZeneca Third Party Product-Specific License granting rights to any intellectual property rights that it has determined are [***] to Exploit a Licensed Product or a Licensed Compound in the U.S., which notice will include (i) any payment obligations directly related to the potential agreement in the U.S. and (ii) a copy of such proposed AstraZeneca Third Party Product-Specific License. The JSC shall review and discuss such proposal. AstraZeneca will [***] any comments provided by Akcea on such potential agreement, but will have the sole right to determine whether to obtain such AstraZeneca Third Party Product-Specific License and the terms of such agreement after discussion at the JSC. If AstraZeneca elects to obtain such AstraZeneca Third Party Product-Specific License, then any financial obligations under such AstraZeneca Third Party Product-Specific License that are reasonably allocable to the Exploitation of a Licensed Product in the U.S. will [***].

11.8.3 Additional Core IP.

(a) Akcea and its Affiliates shall have the first right to obtain and shall be responsible for obtaining a license under any Additional Core IP. If Akcea or its Affiliate obtains a license under any Additional Core IP, then [***] or its applicable Affiliate shall pay [***] under such license and such license will be considered a Future In-License Agreement.

(b) If Akcea or its Affiliates decline to obtain a license under any Additional Core IP pursuant to Section 11.8.3(a) within [***] of receiving notice pursuant to Section 11.8.1, then AstraZeneca shall have the second right to obtain a license under such Third Party intellectual property rights. In such case, if AstraZeneca elects to obtain a license under any such Additional Core IP, then, subject to Section 11.6.2(d), [***] shall pay [***] under such license agreement (except as set forth in Section 11.8.3(c)).

(c) If AstraZeneca elects to obtain a license under any Additional Core IP that is [***] to Exploit the Licensed Product or the Licensed Compound in the U.S. and Akcea has not exercised the Opt-Out Right in accordance with Section 3.6, then any financial obligations under such license that are reasonably allocable to the Exploitation of the Licensed Product in the U.S. will [***].

11.8.4 Future In-License Agreements. Akcea shall, and shall cause its Affiliates to, ensure that all Future In-License Agreements are consistent with the terms and conditions of this Agreement in all material respects and [***], except to the extent that (a) [***] or (b) [***]. Akcea or its applicable Affiliate shall pay [***] under any Future In-License Agreement.

11.9 **Minimum Payments**. During the Royalty Term, in no event will the aggregate royalty reductions under Section 11.6.2 collectively reduce the Opt-Out Scenario One Royalties or the ROW Royalties payable to Akcea on Net Sales of a Licensed Product in any given Calendar Quarter to an amount that is less than [***]% of the amount of Opt-Out Scenario One Royalties or the ROW Royalties, respectively, that would otherwise be due under this Agreement. Notwithstanding the foregoing[***].

11.10 **Other Operating Expenses.**

11.10.1 **Share Ratios**. The Parties will share the Other Operating Expenses incurred with respect to Exploitation of the Licensed Products for the U.S. prior to the Opt-Out Date as follows: Akcea will bear [***]% and AstraZeneca will bear [***]% of all Other Operating Expenses incurred.

11.10.2 **Shared Other Operating Expenses Payment Reconciliation**. Unless and until the Opt-Out Date occurs (and for the Calendar Quarter in which the Opt-Out Date occurs), the following shall apply: No later than [***] after the end of each Calendar Quarter, each Party will deliver to the other Party a written report that sets forth in detail the actual Other Operating Expenses incurred by or on behalf of such Party during such Calendar Quarter (such report of actual expenses, the "***Other Operating Expenses Cost Share Notice***"). Each Party will provide the other Party with supporting documentation of such Other Operating Expenses if reasonably requested by the other Party. For each such Calendar Quarter, no later than [***] after receipt of the Other Operating Expenses Cost Share Notice for such Calendar Quarter from each Party, the Party that incurred less than its allocation of Other Operating Expenses during such Calendar Quarter will make a balancing payment to the other Party to effect the cost-sharing ratios set forth in Section 11.10.1, to the extent the amounts set forth in the Other Operating Expenses Cost Share Notices are undisputed. Any dispute regarding amounts set forth in an Other Operating Expenses Cost Share Notice will be promptly referred to the JSC for resolution, and if the JSC determines that any disputed amount should be included in the applicable Other Operating Expenses Cost Share Notice, the Party that incurred less than its allocation of Other Operating Expenses during such Calendar Quarter (taking into account any balancing payments previously made for such Calendar Quarter pursuant to the immediately preceding sentence) will make a balancing payment to the other Party to effect the cost-sharing ratios set forth in Section 11.10.1 within [***] of the JSC determination.

11.11 **Accounting**.

11.11.1 **General Principles Regarding Eligible Expenses**.

(a) **Consistency with Accounting Treatment**. The Parties acknowledge and agree that expenses will not be reflected in Eligible Expenses unless and until such expenses are recognized by such Party in its statements of profit and loss which are included in its financial statements in accordance with its Accounting Standards, except as expressly provided in the definition of Eligible Expenses.

(b) **General Allocation Principles**.

(i) The allocation method for all Eligible Expenses that are not solely related to the Licensed Product as part of the Development Plan and Budget, U.S. Commercialization Plan and Budget, and U.S. Medical Affairs Plan and Budget will be applied in accordance with the incurring Party's Accounting Standards, consistently applied across its products.

(ii) Included FTE Costs and Expenses will only be included in Eligible Expenses through FTE Costs and will not be separately charged.

(iii) Out-of-Pocket Costs will exclude general and administrative expenses including individuals who perform general and administrative activities within Development, Commercialization and Medical Affairs activities, except as expressly provided in the definition of Eligible Expenses.

(iv) Out-of-Pocket Costs that are associated with the Licensed Product will be directly charged as Eligible Expenses without any markup or overhead added.

11.11.2 Records. Each Party agrees to keep, and to require its Affiliates and, with respect to AstraZeneca, use Commercially Reasonable Efforts to cause its Sublicensees, to keep, complete and accurate records for a minimum period of [***] after the relevant payment is owed pursuant to this Agreement, setting forth Eligible Expenses, COGS, Net Sales of the Licensed Products, and other amounts payable to the other Party hereunder in sufficient detail to enable amounts owed or payable to the other Party hereunder to be determined.

11.11.3 Audits.

(a) Each Party further agrees, that during the Term and for a period of [***] thereafter, upon not less than [***] prior written notice, to permit, and to cause its Affiliates to permit, examination of such books and records relating to the Licensed Product by an independent accounting firm of nationally recognized standing selected by the other Party and reasonably acceptable to such audited Party for the purpose of verifying the accuracy of the accrual of any milestone payments, the calculation and reporting of Net Sales of the Licensed Products, the correctness of any milestone or royalty payment made under this Agreement and the calculation of Eligible Expenses (and cost sharing thereof), for any period within the preceding [***]. Such independent accounting firm shall be subject to appropriate confidentiality provisions substantially equivalent to those of this Agreement. Such audit will not be performed more frequently than [***] period, and will be conducted during normal business hours, in the location where such books and records are normally kept, and otherwise in a manner that minimizes any interference to the audited Party's business operations. The independent accounting firm will only share the results of the audit, not the underlying records, with the auditing Party. The auditing Party will provide the audited Party with a copy of the results of the audit promptly following the auditing Party's receipt thereof.

(b) Such examination is to be made at the expense of the auditing Party, except if the results of the audit reveal an underpayment or overcharge by the audited Party of [***]% or more during the period being audited, then the reasonable fees and expenses for such examination will be paid by the audited Party.

(c) If any audit establishes that the audited Party underpaid or overcharged any amounts due to or from, as applicable, the auditing Party under this Agreement, then, unless disputed pursuant to Section 11.11.3(d), the audited Party shall pay the auditing Party any such deficiency or refund any such overcharged amount within [***] after receipt of a copy of the results of the audit and written notice thereof. If any audit establishes that the audited Party overpaid or undercharged any amounts due to or from, as applicable, the auditing Party under this Agreement, then, unless disputed pursuant to Section 11.11.3(d), the audited Party may offset all such excess payments or undercharged amounts, against any outstanding or future amounts payable by the audited Party to the auditing Party under this Agreement until the audited Party has received full credit for all such excess payments or undercharged amounts; *provided* that if no outstanding or future amounts are payable by the audited Party to the auditing Party under this Agreement, the auditing Party shall pay the audited Party any such excess payment or undercharged amount within [***] after receipt of a copy of the results of the audit and written notice thereof. Interest, as set forth in Section 11.15, will be due on any amounts owed pursuant to this Section 11.11.3(c) or Section 11.11.3(d) if [***].

(d) **Audit Dispute**. In the event of a dispute with respect to any audit under this Section 11.11.3, Akcea and AstraZeneca shall work in good faith to resolve the dispute. If the Parties are unable to reach a mutually acceptable resolution of any such dispute within [***], the dispute shall be submitted for resolution to a certified public accounting firm jointly selected by each Party's certified public accountants or to such other Person as the Parties shall mutually agree (the "***Auditor***"). The decision of the Auditor shall be final and the costs of such arbitration as well as the initial audit shall be borne between the Parties in such manner as the Auditor shall determine. Not later than [***] after such decision and in accordance with such decision, either (i) the audited Party shall pay any underpaid or overcharged amounts (and any interest thereon as set forth in Section 11.15 only if required pursuant to the last sentence of Section 11.11.3(c)) or (ii) the auditing Party shall reimburse any excess payment or undercharged amount (and any interest thereon as set forth in Section 11.15 only if required pursuant to the last sentence of Section 11.11.3(c)).

11.12 Methods of Payments. All payments due from either Party under this Agreement will be paid in Dollars by wire transfer to a U.S. denominated bank account designated in writing by the payee and will be non-creditable (except as otherwise expressly provided in Section 2.4.1(b)(ii), Section 2.4.1(b)(iii), Section 2.5.4, Section 11.11.3(c)), irrevocable and non-refundable, *provided* that the foregoing shall not preclude either Party from claiming the amount of any such payment as Losses in connection with any right or remedy sought by such Party in the event of an actual or threatened breach of this Agreement.

11.13 Taxes. The provisions of this Section 11.13 are to be read in conjunction with the provisions of Section 17.3.

11.13.1 Taxes On Income. Each Party alone will be solely responsible for paying any and all taxes (other than withholding taxes required by applicable Law to be paid by AstraZeneca or Akcea (as the case may be)) levied on account of, or measured in whole or in part by reference to, the income of such Party.

11.13.2 Indirect Taxes.

(a) All payments are exclusive of Indirect Taxes. If any Indirect Taxes are chargeable in respect of any payments, the paying Party will pay such Indirect Taxes at the applicable rate in respect of such payments following receipt, where applicable, of an Indirect Taxes invoice in the appropriate form issued by the receiving Party in respect of those payments.

(b) The Parties will issue invoices for all amounts payable under this Agreement consistent with Indirect Tax requirements and irrespective of whether the sums may be netted for settlement purposes. If such amounts of Indirect Taxes are refunded by the applicable Governmental Authority or other fiscal authority subsequent to payment, the Party receiving such refund will transfer such amount to the paying Party within [***] of receipt. The Parties agree to reasonably cooperate to provide any information required by the Party pursuing a refund of Indirect Taxes paid.

11.13.3 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 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. In accordance with the procedures set forth in Section 15.4, 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.

11.13.4 Tax Cooperation. At least [***] 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 in order 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 applicable Law. 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 11.13.

11.13.5 Prevention of Facilitation of Tax Evasion.

(a) Each Party represents, warrants and undertakes that neither it nor its Affiliates shall commit a tax evasion facilitation offence under Part 3 of the UK Criminal Finances Act 2017 in connection with or attributable to this Agreement or the transactions contemplated hereby.

(b) Each Party shall promptly report to the other Party any apparent breach of Section 11.13.5(a) and shall (i) answer, in reasonable detail, any written or oral inquiry from the other Party related to its and its Affiliates compliance with Section 11.13.5(a), (ii) facilitate the interview of employees of such Party by the other Party (or any agent of such Party) at any reasonable time specified by the inquiring Party related to such Party's compliance with Section 11.13.5(a) and (iii) co-operate with the inquiring Party and any Governmental Authority in relation to any investigation relating to the matters referred to in Section 11.13.5(a), in all cases, as reasonably required to enable that other Party to comply with its undertaking in Section 11.13.5(a).

11.14 Currency Exchange. Notwithstanding anything to the contrary in the Agreement, conversion of sales recorded in local currencies to Dollars will be performed using AstraZeneca's, its Affiliate's or its or their Sublicensee's, as applicable, Exchange Rate. "***Exchange Rate***" means the IFRS-compliant rate as used by AstraZeneca Plc for the purpose of preparing its consolidated financial statements on any date, as may be adjusted from time to time, which, as of the Execution Date, is the rate of exchange as published by Reuters as prevailing at 8.00 am (GMT) taken on the 25th day of the month prior to such date, where that day is a Business Day, or if the 25th day of the month is not a Business Day, the first Business Day following the 25th day of the month.

11.15 Interest. If any undisputed payment due to either Party under this Agreement is not paid when due, then such paying Party shall pay interest thereon (before and after any judgment) at an annual rate (but with interest accruing on a daily basis) of [***] the U.S. effective federal funds rate, as adjusted each Business Day and published by the Federal Reserve Bank of New York through its website (https://apps.newyorkfed.org/markets/autorates/fed%20funds) (or in the event that the U.S. effective federal funds rate is no longer an applicable reference rate, such reasonably equivalent alternative as may be selected by AstraZeneca in its reasonable discretion), such interest to run from the date on which payment of such undisputed sum became due until payment thereof in full together with such interest. Notwithstanding the previous sentence, the payable interest rate shall never be less than [***].

ARTICLE 12
INTELLECTUAL PROPERTY

12.1 Ownership of Inventions; Disclosure; Cross-License.

12.1.1 Existing IP. Nothing in this Agreement will affect Akcea's ownership of the Licensed Technology existing as of the Execution Date or AstraZeneca's ownership of AstraZeneca IP existing as of the Execution Date, which in each case will remain owned by the Party having such rights.

12.1.2 Ownership.

(a) **AstraZeneca Program Technology**. As between the Parties, AstraZeneca is the sole owner of any Know-How conceived, discovered, invented or created solely by or on behalf of AstraZeneca or its Affiliates or its or their Sublicensees under or in connection with this Agreement, any Patent Rights that claim or Cover inventions made solely by or on behalf of AstraZeneca or its Affiliates or its or their Sublicensees under or in connection with this Agreement (collectively, the "***AstraZeneca Program Technology***"), and any Trademark(s) for the Licensed Product, and will own and retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by AstraZeneca to Akcea under this Agreement.

(b) **Akcea Program Technology**. As between the Parties, Akcea is the sole owner of any Know-How conceived, discovered, invented or created solely by or on behalf of Akcea or its Affiliates under or in connection with this Agreement and any Patent Rights that claim or Cover inventions made solely by or on behalf of Akcea or its Affiliates under or in connection with this Agreement (collectively, the "***Akcea Program Technology***"), and will own and retain all of its rights, title and interest thereto, subject to any rights or licenses expressly granted by Akcea to AstraZeneca under this Agreement.

(c) **Joint Program Technology**. As between the Parties, the Parties will jointly own any Know-How conceived, discovered, invented or created jointly by or on behalf of both Akcea or its Affiliates, on the one hand, and AstraZeneca or its Affiliates, on the other hand, under or in connection with this Agreement ("***Joint Know-How***") and any Patent Rights that claim or Cover inventions made jointly by or on behalf of both Akcea or its Affiliates, on the one hand, and AstraZeneca or its Affiliates, on the other hand, under or in connection with this Agreement ("***Joint Patent Rights***", and collectively with any Joint Know-How, the "***Joint Program Technology***"). Subject to the licenses granted under this Agreement and the exclusivity obligations set forth in Article 9, each Party will be free to practice and Exploit, either itself or through the grant of licenses to Third Parties (which Third Party licenses may be further sublicensed), the Joint Program Technology throughout the world without restriction, without the need to obtain further consent from or provide notice to the other Party, and without any duty to account or otherwise make any payment of any compensation to the other Party. Each Party shall promptly disclose to the other Party in writing, and shall cause its Affiliates and its and their licensees and (sub)licensees/Sublicensees to so disclose, the conception, discovery, invention or creation of any Joint Know-How or Joint Patent Rights.

(d) **United States Law**. The determination of whether Know-How is conceived, discovered, invented or created by a Party for the purpose of allocating proprietary rights (including Patent Right, copyright, or other intellectual property rights) therein, shall, for purposes of this Agreement, be made in accordance with applicable Law in the United States (without regard to conflict of laws) as such law exists as of the Execution Date irrespective of where such conception, discovery, invention, or creation occurs.

12.1.3 Cross-License.

(a) Subject to the terms and conditions of this Agreement and effective as of the Closing Date, Akcea hereby grants to AstraZeneca, and AstraZeneca accepts, a non-exclusive, royalty-free, fully-paid, perpetual, irrevocable, non-transferable (except in accordance with Section 17.3), sublicensable license under the Akcea Program Technology that is conceived, discovered, invented or created in the performance of Development or Commercialization activities for which the Parties share Eligible Expenses under this Agreement for any and all purposes.

(b) Subject to the terms and conditions of this Agreement and effective as of the Closing Date, AstraZeneca hereby grants to Akcea, and Akcea accepts, a non-exclusive, royalty-free, fully-paid, perpetual, irrevocable, non-transferable (except in accordance with Section 17.3), sublicensable license under the AstraZeneca Program Technology that is conceived, discovered, invented or created in the performance of Development or Commercialization activities for which the Parties share Eligible Expenses under this Agreement for any and all purposes.

12.2 Filing, Prosecution and Maintenance of Patents.

12.2.1 Patent Rights.

(a) **Akcea Core Technology Patent Rights and Akcea Manufacturing Patent Rights**. As between the Parties, Akcea will control and be responsible for Prosecuting and Maintaining (i) the Akcea Core Technology Patent Rights, and (ii) Akcea Manufacturing Patent Rights. Notwithstanding the foregoing, (x) except with respect to the Akcea Product-Specific Patent Rights and Joint Patent Rights as provided herein and as provided in clause (y) below, Akcea will not, and will ensure that its Affiliates and (sub)licensees do not, Prosecute and Maintain any claim in a Patent Right specifically claiming the Licensed Compound or the Exploitation thereof, and (y) with respect to any Akcea Core Technology Patent Rights that include a claim directed specifically to the Licensed Compound and that have been filed and are being Prosecuted and Maintained as of the Execution Date, Akcea will, or will cause its Affiliates to, file divisionals or pursue other similar procedures with respect thereto in a manner so that any such claims are included in Akcea Product-Specific Patent Rights, and to the extent Akcea is unable to do so, Akcea and AstraZeneca will promptly discuss in good faith and, unless otherwise agreed by the Parties, Akcea will, and will cause its Affiliates and (sub)licensees to, cancel such claims and promptly notify AstraZeneca thereof, in each case, so that no Akcea Core Technology Patent Right includes any such claims.

(b) **Akcea Product-Specific Patent Rights**. Following the Closing Date (and so long as the applicable license to AstraZeneca under Section 8.1 is in effect), AstraZeneca will control and be responsible for Prosecuting and Maintaining the Akcea Product-Specific Patent Rights in the Territory.

(c) **Joint Program Technology**. In the event the Parties make any Joint Know-How, the Parties will promptly meet to discuss and determine, based on mutual consent, whether to seek patent protection thereon. Neither Party will file any Joint Patent Right without mutual consent. If the Parties decide to seek patent protection for any Joint Know-How, then [***] will have the first right, but not the obligation, for Prosecuting and Maintaining any Joint Patent Right in the Territory in accordance with the provisions of Section 12.2.2. Where [***] declines to exercise its first right to file on a Joint Patent Right that the Parties have agreed to file, [***] shall have the right for Prosecuting and Maintaining such Joint Patent Right in accordance with the provisions of Section 12.2.2. The non-filing Party will reimburse the filing Party for [***]% of the costs incurred by the filing Party in Prosecuting and Maintaining such Joint Patent Rights, which reimbursement will be made pursuant to, and within [***] of, invoices (including reasonable supporting documentation) submitted by the filing Party to the non-filing Party no more often than once per Calendar Quarter. The non-prosecuting Party will cooperate with the prosecuting Party in taking reasonable measures to control costs and non-prosecuting Party shall be responsible for [***]% of (i) any fees or costs related to any correspondence of outside counsel with or instructions to outside counsel by such Party (or any of such Party's representatives) which is independent of joint prosecution efforts, or (ii) any patent office fees, and associated counsel/agent fees and costs, for extensions which are not incurred at the request of, and not due to the actions of, the prosecuting Party. If either Party (the "***Declining Party***") at any time declines to participate in the Prosecution and Maintenance of any Joint Patent Right or share in the costs of Prosecution and Maintenance of any Joint Patent Right in a country, on a country-by-country basis, the Declining Party will provide the other Party (the "***Continuing Party***") with [***] prior written notice to such effect, in which event, the Declining Party will (A) have no responsibility with respect to the Prosecution and Maintenance of the applicable Joint Patent Right in such country after the end of such [***] period, (B) have no responsibility for any expenses incurred in connection with the Prosecution and Maintenance of such Joint Patent Right in such country after the end of such [***] period and (C) if the Continuing Party elects to continue such Prosecution and Maintenance, then the Declining Party, upon the Continuing Party's request, will execute such documents and perform such acts, at the Continuing Party's expense, as may be reasonably necessary (1) to assign to the Continuing Party all of the Declining Party's right, title and interest in and to such Joint Patent Right in such country and (2) to permit the Continuing Party to Prosecute and Maintain such Joint Patent Right in such country at its sole expense. Where such Joint Patent Right is assigned to AstraZeneca as the Continuing Party, it will be deemed to be AstraZeneca Patent Rights (to the extent it meets the definition of AstraZeneca Patent Rights) and AstraZeneca Program Technology, and will be subject to the applicable license grants to Akcea under this Agreement; and where such Joint Patent Right is assigned to Akcea as the Continuing Party, it will be deemed to be Licensed Technology (to the extent it meets the definition of Licensed Technology) and Akcea Program Technology, and will be subject to the applicable license grants to AstraZeneca under this Agreement.

(d) **AstraZeneca Patent Rights**. AstraZeneca will control and be responsible for Prosecuting and Maintaining the AstraZeneca Patent Rights.

12.2.2 Other Matters Pertaining to Prosecution and Maintenance of Patents. Except with respect to AstraZeneca Patent Rights:

(a) Each Party will keep the other Party informed as to material developments with respect to the Prosecution and Maintenance of the Patent Rights for which such Party has responsibility for Prosecution and Maintenance pursuant to Section 12.2.1, including by providing copies of any material correspondence that such Party provides to or receives from any patent office, including notice of all interferences, reissues, re-examinations, *inter partes* reviews, post-grant reviews, 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) With respect to Prosecution and Maintenance activities under Section 12.2.1(b) or Section 12.2.1(c), AstraZeneca may use counsel of its own choice reasonably acceptable to Akcea (for clarity, it is agreed that AstraZeneca may use internal patent counsel and agents, filing clerks, and paralegals employed by AstraZeneca) for Prosecuting and Maintaining and coordinating worldwide filings of such Patent Rights. At AstraZeneca's request, Akcea will cooperate and assist AstraZeneca and outside counsel and agents in the Prosecution and Maintenance of such Patent Rights. Subject to Section 12.9, if AstraZeneca elects (i) not to file and prosecute patent applications for an Akcea Product-Specific Patent Right ("***AstraZeneca Prosecuted Patents***") in a particular country, (ii) not to continue the prosecution (including any interferences, oppositions, reissue proceedings, or re-examinations) or maintenance of any AstraZeneca Prosecuted Patent in a particular country, or (iii) not to file and prosecute patent applications for the AstraZeneca Prosecuted Patent in a particular country following a written request from Akcea to file and prosecute in such country, then AstraZeneca will so notify Akcea promptly in writing of its intention not less than [***] before an action is required to enable Akcea to meet any deadlines by which an action must be taken to establish or preserve any such Patent Right in such country; and Akcea will have the right, but not the obligation, to file, prosecute and maintain such AstraZeneca Prosecuted Patent in the applicable country at its own expense with counsel of its own choice; *provided* that Akcea shall ensure that its filing, prosecution and maintenance of such AstraZeneca Prosecuted Patent in such country is consistent with AstraZeneca's Prosecution and Maintenance of such AstraZeneca Prosecuted Patent in other countries and is not reasonably likely to adversely affect the scope, validity or enforceability of such AstraZeneca Prosecuted Patent in other countries or any of the other Patent Rights being Prosecuted and Maintained by AstraZeneca under this Agreement. In such a case, AstraZeneca will cooperate with Akcea to file for, or continue to prosecute and maintain such AstraZeneca Prosecuted Patent in such country in Akcea's own name, but only to the extent that AstraZeneca is not required to take any position with respect to such abandoned AstraZeneca Prosecuted Patent that is inconsistent with AstraZeneca's Prosecution and Maintenance of such AstraZeneca Prosecuted Patent in other countries or that would be reasonably likely to adversely affect the scope, validity or enforceability of any of such AstraZeneca Prosecuted Patent in other countries or the other Patent Rights being Prosecuted and Maintained by AstraZeneca under this Agreement. Notwithstanding anything to the contrary in this Agreement, if Akcea assumes responsibility for the prosecution and maintenance of the any such AstraZeneca Prosecuted Patent under this Section 12.2.2(b), then Akcea will have no obligation to notify AstraZeneca if Akcea intends to abandon such AstraZeneca Prosecuted Patent.

12.2.3 Patent Costs. Except as set forth in Section 12.2.1(c) and Section 12.2.2 or to the extent costs are included in the definition of an Eligible Commercialization Expense, each Party will be responsible for all patent costs incurred by such Party after the Closing Date in all countries designated by it in the Prosecution and Maintenance of Patent Rights for which such Party is responsible under Article 12.

12.3 Defense of Claims Brought by Third Parties; Oppositions.

12.3.1 Licensed Compound. If a Third Party initiates a proceeding against a Party claiming a Patent Right owned by or licensed to such Third Party is infringed by the Exploitation of any Licensed Compound or Licensed Product in the Territory, then AstraZeneca will have the first right, but not the obligation, to defend against any such proceeding at its sole cost and expense (except to the extent shared as Third Party Payments under this Agreement). If AstraZeneca elects to defend against such proceeding, then AstraZeneca will have the sole right to direct the defense and to elect whether to settle such claim (but, prior to Akcea's exercise of the Opt-Out Right, only with the prior written consent of Akcea for any such claims that are related to the U.S., not to be unreasonably withheld, conditioned or delayed). AstraZeneca will keep Akcea apprised of the progress of such proceeding. If AstraZeneca elects not to defend against a proceeding, then AstraZeneca will so notify Akcea in writing within [***] after AstraZeneca first receives written notice of the initiation of such proceeding, and Akcea will have the right, but not the obligation, to defend against such a proceeding at its sole cost and expense and thereafter Akcea will have the sole right to direct the defense thereof, including the right to settle such claim, but only with the prior written consent of AstraZeneca, which consent will not be unreasonably withheld, delayed or conditioned. In any event, the Party not defending such proceeding will reasonably assist the other Party and cooperate in any such litigation at the defending Party's request and expense. 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 12.3.1. Each Party will provide the other Party with prompt written notice of the commencement of any such proceeding under this Section 12.3.1, 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.

12.3.2 Interferences, Reissues, Re-Examinations and Oppositions. If a Third Party initiates a proceeding related to an interference, reissue, re-examination or opposition of an Akcea Product-Specific Patent Right or Joint Patent Right in the Territory, the Party responsible for Prosecution and Maintenance pursuant to Section 12.2.1 will, by written notice to the other Party, either (a) control the defense of such proceeding or (b) give the other Party the right to control the defense of such proceeding, in each case ((a) and (b)), solely to the extent such proceeding relates to an interference, reissue, re-examination or opposition of an Akcea Product-Specific Patent Right or Joint Patent Right, *provided* that if the Party responsible for Prosecution and Maintenance pursuant to Section 12.2.1 makes no such election within [***], then the other Party will have the right, but not the obligation, to control the defense of such proceeding, at such other Party's sole expense. In any event, the Party not defending such proceeding will reasonably assist the other Party and cooperate in any such litigation at the defending Party's request and expense. 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 12.3.2. Each Party will provide the other Party with prompt written notice of the commencement of any such proceeding under this Section 12.3.2, 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.

12.4 Enforcement of Patents Against Competitive Infringement. With respect to infringement, unauthorized use, misappropriation or threatened infringement by a Third Party of any Akcea Product-Specific Patent Rights or Joint Patent Rights by reason of the Exploitation of a product that binds to TTR anywhere in the Territory ("***Competitive Infringement***"), the Parties will handle such Competitive Infringement in accordance with the remainder of this Section 12.4.

12.4.1 Duty to Notify of Competitive Infringement. If either Party learns of a Competitive Infringement by a Third Party in the Territory, then 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 12.4.5 below, such written notice will be given within [***] after learning of such Competitive Infringement.

12.4.2 Control of Competitive Infringement Proceedings. AstraZeneca will have the first right, but not the obligation, to institute, prosecute, and control and settle a proceeding with respect to a Competitive Infringement, including as a defense or counterclaim in connection with any proceeding regarding Third Party infringement under Section 12.3.1, by counsel of its own choice at its own cost and expense (except to the extent included in the definition of Other Operating Expenses), and Akcea will have the right, at its own cost and expense, to be represented in that action by counsel of its own choice (which amounts shall not be included in Other Operating Expenses), *however*, AstraZeneca will have the right to control (including the right to settle) such litigation. If AstraZeneca fails to initiate a proceeding within a period of [***] after receipt of written notice of such Competitive Infringement (subject to a [***] extension to conclude negotiations, if AstraZeneca has commenced good faith negotiations with an alleged infringer for elimination of such Competitive Infringement within such [***] period), then Akcea will have the right to initiate and control a proceeding with respect to such Competitive Infringement by counsel of its own choice at its own cost and expense (except to the extent included in the definition of Other Operating Expenses), and AstraZeneca will have the right to be represented in any such action by counsel of its own choice at its own cost and expense (which amounts shall not be included in Other Operating Expenses). Notwithstanding the foregoing, if [***]; *provided, however*, that [***].

12.4.3 Joinder; Cooperation.

(a) If a Party initiates a proceeding in accordance with this Section 12.4, 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 12.4.4, the costs and expenses of each Party incurred pursuant to this Section 12.4.3(a) will be borne by the Party initiating such proceeding.

(b) If one Party initiates a proceeding in accordance with this Section 12.4, 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.

12.4.4 Share of Recoveries. Any damages or other monetary awards recovered with respect to a proceeding brought pursuant to Section 12.4 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, except that such Out-of-Pocket Costs that were shared between the Parties as Other Operating Expenses and for which reconciliation payments have been made pursuant to Section 11.10 will be applied to each Party to the extent of its respective share of such Other Operating Expenses (and provided that amounts will be allocated *pro rata* if insufficient to cover the totality of such Out-of-Pocket Costs);

(b) if Akcea has not exercised its Opt-Out Right, then the amount of such recovery that relates to a Competitive Infringement in the U.S. will then be shared by the Parties, with AstraZeneca receiving [***]% of such remaining proceeds and Akcea receiving [***]% of such remaining proceeds; and

(c) any other proceeds (either because such proceeds were the result of a Competitive Infringement outside the U.S. or because Akcea has exercised its Opt-Out Right) will be allocated as follows: (i) [***] or (ii) [***].

12.4.5 35 USC § 271(e)(2) Infringement. Notwithstanding anything to the contrary in this Section 12.4, for a Competitive Infringement under 35 USC § 271(e)(2), the time period set forth in Section 12.4.2 during which AstraZeneca will have the initial right to bring a proceeding will be shortened to a total of [***], so that, to the extent Akcea has the right, pursuant to such Section 12.4.2 to initiate a proceeding if AstraZeneca does not initiate a proceeding, Akcea will have such right if AstraZeneca does not initiate a proceeding within [***] after AstraZeneca's receipt of written notice of such Competitive Infringement.

12.5 Settlement. Notwithstanding anything to the contrary in this Article 12, neither Party may enter a settlement, consent judgment or other voluntary final disposition of a suit under this Article 12 that (a) 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 or its Affiliates (*provided* that, with respect to AstraZeneca as the settling Party, the foregoing shall not apply to Akcea Product-Specific Patent Rights), or (b) imposes any costs or liability on, or involves any admission of wrongdoing by the other Party or its Affiliates, in each case without first obtaining the written consent of the other Party; *provided* that a settlement of Competitive Infringement that would or may result in reduced payments hereunder shall not, in and of itself, be deemed to require the consent of such other Party.

12.6 Patent Listing. AstraZeneca will have the sole right, at its discretion (except as set forth in this Section 12.6), to list, with the applicable Regulatory Authorities commencing on the Closing Date and during the remainder of the Term, all applicable Akcea Patent Rights. Prior to such listings, the Parties will meet to evaluate and identify all applicable Patent Rights, and AstraZeneca will have the right to review, where reasonable, original records relating to any invention for which Patent Rights are being considered by AstraZeneca for any such listing. Notwithstanding the preceding sentence, AstraZeneca will retain final decision-making authority as to the listing of all applicable Akcea Patent Rights for the Licensed Product that are not Akcea Core Technology Patent Rights or Akcea Manufacturing Patent Rights, regardless of which Party owns such Patent Rights, and AstraZeneca may not list any Akcea Core Technology Patent Rights or Akcea Manufacturing Patent Rights unless the Parties mutual agree to do so, or unless otherwise required by applicable Law.

12.7 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, then it will notify the other Party and neither Party will make an election under such provision when exercising its rights under this Article 12 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).

12.8 **Additional Rights and Exceptions**. Other than as expressly set forth in this Article 12, as between the Parties, Akcea retains the sole right to (a) Prosecute and Maintain (i) Akcea Core Technology Patent Rights and (ii) Akcea Manufacturing Patent Rights during the Term, and (b) control any enforcement of Akcea Core Technology Patent Rights and Akcea Manufacturing Patent Rights, *provided* that if under clause (b) the enforcement of Akcea Core Technology Patent Rights or Akcea Manufacturing Patent Rights is believed in AstraZeneca's reasonable opinion to potentially impact Net Sales and such an Akcea Core Technology Patent Right or Akcea Manufacturing Patent Right is the only Akcea Patent Right Covering the Licensed Product at the time of such enforcement proceeding, then AstraZeneca has the second right, but no obligation, to enforce such patents, *so long as* AstraZeneca, in connection with any such enforcement proceeding, also enforces any relevant AstraZeneca Patent Rights. Any damages or other monetary awards recovered with respect to a proceeding brought pursuant to clause (b) of this Section 12.8 that impacts Net Sales will be shared as follows:

12.8.1 any recoveries will first be applied to reimburse each Party's reasonable Out-of-Pocket Costs incurred in connection therewith (which amounts will be allocated *pro rata* if insufficient to cover the totality of such Out-of-Pocket Costs); and

12.8.2 any remaining recoveries will be [***].

12.9 **Patent Term Extension**. Notwithstanding Section 12.2.2(b), the Parties will cooperate with each other in gaining Patent Term Extension with respect to Akcea Product-Specific Patent Rights wherever applicable to the Licensed Product, and AstraZeneca will determine which Akcea Product-Specific Patent Rights will be extended and will have the exclusive right, but not the obligation, to seek such Patent Term Extension, in Akcea's or Ionis's name, if so required.

12.10 **UPC**. With respect to any Akcea Product-Specific Patent Rights, AstraZeneca will have the right to determine whether to opt in or opt out (and to opt in again) of the Unified Patent Court system and if requested by AstraZeneca, Akcea will promptly do all things reasonably necessary and execute all documents required to give effect to such decision(s), provided that [***].

ARTICLE 13
CONFIDENTIALITY

13.1 **Confidentiality; Exceptions**. Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that the receiving Party and its Affiliates (the "***Receiving Party***") 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) that is disclosed to it by the other Party or its Affiliates (the "***Disclosing Party***"), including trade secrets, Know-How, inventions or discoveries, proprietary information, data of a financial, commercial or technical nature, formulae, processes, techniques and information relating to the Disclosing Party's past, present or future marketing, financial or Exploitation activities of any product or potential product or useful technology of the Disclosing Party or the pricing thereof (collectively, "***Confidential Information***"), except to the extent that it can be established by the Receiving Party that such Confidential Information:

13.1.1 was in the lawful knowledge and possession of the Receiving Party prior to the time it was first disclosed to the Receiving Party by the Disclosing Party, or was otherwise developed independently by the Receiving Party without reference to any of the Disclosing Party's Confidential Information, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party; *provided* that the foregoing exception shall not apply with respect to Akcea Product-Specific IP or Joint Know-How;

13.1.2 was generally available to the public or otherwise part of the public domain at the time of its first disclosure to the Receiving Party by the Disclosing Party;

13.1.3 became generally available to the public or otherwise part of the public domain after its disclosure to the Receiving Party by the Disclosing Party and other than through any act or omission of the Receiving Party in breach of this Agreement; or

13.1.4 was disclosed to the Receiving Party, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party not to disclose such information to others.

The Receiving Party will protect all Confidential Information against unauthorized disclosure to Third Parties with the same degree of care as the Receiving Party uses for its own similar information, but in no event less than a reasonable degree of care. The Joint Know-How and the terms and conditions of this Agreement and following the Closing Date, the Akcea Product-Specific IP shall be deemed to be the Confidential Information of both of the Parties hereto and shall be deemed to have been disclosed by Akcea to AstraZeneca, on the one hand, and by AstraZeneca to Akcea, on the other hand; *provided* that if this Agreement is earlier terminated in accordance with Section 16.2, then the Akcea Product-Specific IP will thereafter be deemed to be Confidential Information of Akcea only.

13.2 **Prior Confidentiality Agreement Superseded**. This Agreement supersedes the Mutual Confidential Disclosure Agreement executed by Ionis and AstraZeneca on March 5, 2021 (including any and all amendments thereto). All information exchanged by the Parties under such Mutual Confidential Disclosure Agreement is deemed Confidential Information hereunder and subject to the terms of this Article 13.

13.3 **Authorized Disclosure**. The Receiving Party may only use the Confidential Information of the Disclosing Party for exercising its rights and performing its obligations under this Agreement and may only disclose Confidential Information of the Disclosing Party as follows: (a) to the extent required to its Affiliates and its and their respective directors, officers, employees, agents, existing or prospective sublicensees, permitted assignees, consultants and representatives who reasonably need to know such Confidential Information in order to advise or assist the Receiving Party in connection with the performance of its obligations or rights granted or reserved in this Agreement and under appropriate confidentiality provisions substantially equivalent to those of 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; (b) to the extent reasonably necessary to file or prosecute patent, copyright and trademark applications or to obtain or maintain Regulatory Approvals as permitted under this Agreement; (c) as required by applicable Law or in response to a valid Order of a court of competent jurisdiction; *provided, however*, that if a Receiving Party is required by Law or in response to a valid Order of a court to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable, give reasonable advance notice to the Disclosing Party of such disclosure requirement, limit disclosure to only the Confidential Information requested to be disclosed and, if requested by the Disclosing Party, cooperate with the Disclosing Party to secure confidential treatment of such Confidential Information required to be disclosed; (d) in communication with existing or prospective investors, lenders, financing sources, professional advisors, acquirers, merger partners, subcontractors, licensees or Inbound Licensors (to the extent required by the applicable In-License Agreement) on a need to know basis, in each case under appropriate confidentiality provisions substantially equivalent to those of this Agreement; (e) to the extent mutually agreed to in writing by the Parties; or (f) (i) with respect to AstraZeneca as the Receiving Party, as may be necessary or useful in connection with the Exploitation of the Licensed Compound and Licensed Product, and (ii) with respect to Akcea as the Receiving Party, as may be necessary or useful in connection with the performance of its Development activities pursuant to the Development Plan and Budget or its Co-Commercialization and Medical Affairs Activities. The confidentiality and non-use obligations set forth under this Agreement will survive the termination or expiration of this Agreement for a period of five years.

13.4 **Press Release; Disclosure of Agreement**. On or promptly after the Execution Date, each Party will issue a press release of the execution of this Agreement, the content of which shall be mutually agreed to in writing by the Parties. Subject to Section 13.5, neither Party may issue any other press release or other public disclosure regarding this Agreement or its terms or the Parties' activities hereunder, or any results or data arising hereunder, except (a) with the other Party's prior written consent (such consent not to be unreasonably withheld, conditioned or delayed), or (b) for any disclosure that is, in the opinion of the disclosing Party's counsel, reasonably necessary to comply with applicable securities exchange listing requirements or other applicable Laws. Each Party will provide to the other Party a copy of any public announcement regarding this Agreement or the subject matter hereof (including any filing with the United States Securities and Exchange Commission (or any stock exchange, including Nasdaq, or any similar regulatory agency in any country other than the United States)), as practicable under the circumstances, reasonably prior to its scheduled release (and in any event less than [***] prior to the anticipated date of disclosure). Each Party will have the right to expeditiously review and recommend changes to any such announcement, and, except as otherwise required by securities exchange listing requirements or applicable Law, the Party whose announcement has been reviewed will remove any Confidential Information of the reviewing Party that the reviewing Party reasonably deems to be inappropriate for disclosure and will give due consideration to any reasonable comments by the reviewing Party relating to such announcement, including the provisions of this Agreement for which confidential treatment should be sought. For clarity, the Parties hereby acknowledge and agree that each Party may file this Agreement under the Securities Act in the United States and that the Parties will each use reasonable efforts to obtain confidential treatment of the commercial terms and sensitive technical and any other portions of this Agreement that such other Party requests be kept confidential. Notwithstanding the foregoing, to the extent information regarding this Agreement has already been publicly disclosed, each Party (other than a Party that had caused such information to become publicly disclosed in breach of this Article 13) may subsequently disclose the same information to the public without the consent of the other Party, *provided* that such information remains accurate at the time of such subsequent disclosure.

13.5 **Publications**. Except as expressly permitted in this Section 13.5, neither Party nor its Affiliates or sublicensees will publish or publicly disclose the scientific results of any of the activities conducted with respect to the Licensed Compound or Licensed Product without the prior written consent of the other Party. The Parties recognize that it may be useful or required to publish or publicly disclose the results of Exploitation activities conducted with respect to the Licensed Compound or Licensed Product, and each Party (and its Affiliates and sublicensees) will be free to publish or publicly disclose such results, including on its clinical trials registry or on a government-sponsored database such as www.clinicaltrials.gov, subject to the prior review by the other Party for patentability and protection of its Confidential Information as described in this Section 13.5 and, in the case of [***] as the publishing Party, only with [***] prior written consent (not to be unreasonably withheld, conditioned or delayed). The Party that desires to publish such results will provide the other Party with a copy of such proposed abstract, manuscript, or presentation no less than [***] ([***] in the case of abstracts) prior to its intended submission for publication. The reviewing Party will respond in writing promptly and in no event later than [***] ([***] in the case of abstracts) after receipt of the proposed material, with one or more of the following: (a) comments on the proposed material, which the publishing Party will consider in good faith, (b) a specific statement of concern, based upon the need to seek patent protection or to block publication if the reviewing Party determines that the proposed disclosure contains or describes intellectual property that should be maintained as a trade secret to protect the Licensed Product or any Exploitation activities conducted under this Agreement, or (c) an identification of the reviewing Party's Confidential Information that is contained in the material reviewed. In the event of concern over patent protection or whether maintaining a trade secret would be a priority, the publishing Party agrees not to submit such publication or to make such presentation that contains such information until the reviewing Party is given a reasonable period of time, and in no event more than [***], to seek patent protection for any material in such publication or presentation which it believes is patentable or to resolve any other issues. All publications made by either Party shall be consistent with the publication strategy included in the U.S. Medical Affairs Plan and Budget. Notwithstanding anything herein to the contrary, Akcea and, its Affiliates may publish or publicly disclose any scientific data or results with respect to the Clinical Trial that is ongoing as of the Execution Date for [***] without the prior consent of AstraZeneca; *provided* that (i) prior to publication by Akcea and its Affiliates (if applicable), AstraZeneca will have the right to review and approve the content of such publications, which approval of the contents will not be unreasonably withheld, conditioned or delayed and (ii) Akcea shall ensure such publication is made within [***] after Completion of such Clinical Trial.

13.6 **Remedies**. 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 injunction, without the posting of any bond or other security, enjoining or restraining the other Party from any violation or threatened violation of this Article 13.

13.7 **Ongoing Obligation for Confidentiality**. Upon the effective date of termination of this Agreement, upon the Disclosing Party's request, the Receiving Party shall destroy or return (as requested by the Disclosing Party) any Confidential Information of the Disclosing Party (in the event of termination of this Agreement with respect to one or more Terminated Territories but not in its entirety, solely to the extent relating specifically and exclusively to such Terminated Territories), except that the Receiving Party (a) may retain a single copy of the Confidential Information for the sole purpose of (i) ascertaining its rights and responsibilities in respect of such Confidential Information and (ii) exercising its rights that expressly survive the expiration or termination of this Agreement and (b) shall not be required to destroy any computer files stored securely by the Receiving Party that are created by automatic system back up.

13.8 **Use of Name; Acknowledgment**. Except as otherwise set forth in this Section 13.8, neither Party will use the other Party's name, logo or Trademark in a press release or other publication or other form of publicity without first obtaining the prior consent of the Party to be named. Each Party will acknowledge in any press release, public presentation or publication regarding the collaboration or the Licensed Product, the other Party's role in discovering and developing the Licensed Product, that the Licensed 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; NYSE: AZN). Ionis may include the Licensed Product (and identify AstraZeneca as its partner for the Licensed Product) in Ionis' drug pipeline.

ARTICLE 14
REPRESENTATIONS AND WARRANTIES

14.1 **Representations and Warranties of the Parties**. Each Party hereby represents and warrants to the other Party, as of the Execution Date and as of the Closing Date, that:

14.1.1 such Party is duly organized, validly existing and in good standing under the Laws of the jurisdiction of its incorporation and has full corporate power and authority to enter into and deliver this Agreement and to carry out the provisions hereof;

14.1.2 such Party has taken all necessary action on its part required by applicable Law and its organizational documents to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

14.1.3 this Agreement has been duly and validly executed and delivered on behalf of such Party, and, assuming due and valid authorization, execution and delivery by the other Party, constitutes a legal, valid, and binding obligation, enforceable against it in accordance with the terms hereof, subject to bankruptcy, insolvency, moratorium or other similar Laws affecting or relating the enforcement of creditors' rights generally, and general principles of equity;

14.1.4 the execution, delivery and performance of this Agreement by such Party does not conflict with any agreement or any provision thereof, or any instrument or understanding, oral or written, to which it is a party or by which it is bound, nor violate any Law or regulation of any Governmental Authority having jurisdiction over such Party;

14.1.5 except as contemplated by Section 10.2, all consents, approvals and authorizations from all Governmental Authorities or other Third Parties required to be obtained by such Party in connection with this Agreement have been obtained;

14.1.6 such Party is not debarred under the United States Federal Food, Drug and Cosmetic Act or comparable applicable Laws; and

14.1.7 (a) none of a Party's officers, directors and employees, and to each Party's Knowledge, any other Person acting on its behalf, has directly or indirectly given, offered or promised to give money or anything of value to any Government Official in an effort to influence any Government Official or any other Person in a corrupt or improper effort to obtain or retain business or any commercial advantage, such as a permit or license to do business, or accepted such a payment, and (b) all Persons acting on its behalf have materially complied with all applicable Laws in connection with conducting its business operations, including the U.S. Foreign Corrupt Practices Act, laws implementing the Convention on Combating Bribery of Foreign Public Officials in International Business Transactions and local Laws prohibiting bribery, kickbacks, or other unlawful or improper means of obtaining business or commercial advantages, in each case ((a) and (b)), (i) as to Akcea, with respect to the Licensed Compound or Licensed Product, and (ii) as to AstraZeneca, that would, in the reasonable view of AstraZeneca, have a material adverse effect on Akcea.

14.2 **Representations and Warranties of Akcea**. Akcea hereby represents and warrants to AstraZeneca, as of the Execution Date and as of the Closing Date, and covenants, that:

14.2.1 Akcea has all rights, authorizations and consents necessary to grant all rights and licenses it purports to grant to AstraZeneca with respect to the Licensed Technology under this Agreement, in each case, free and clear of any rights of any Third Party that would be in conflict with the licenses and other rights it purports to grant to AstraZeneca under this Agreement and has obtained the prior written consent of Ionis as required under the Ionis/Akcea Agreement with respect to the grant of such rights and licenses;

14.2.2 Akcea has sufficient legal or beneficial title and ownership or right to license (or sublicense as the case may be) with respect to the Licensed Technology as is necessary to fulfill its obligations under this Agreement and to grant the licenses (or sublicenses as the case may be) to AstraZeneca pursuant to this Agreement;

14.2.3 there is no (a) action, suit, claim, demand, dispute, proceeding, arbitration, inquiry, investigation or other legal action of any nature, civil, criminal, regulatory or otherwise, pending or, to Akcea's Knowledge, threatened, against Akcea or any of its Affiliates or (b) judgement or settlement against or owed by Akcea or any of its Affiliates, in each case ((a) and (b)) in connection with the Licensed Technology, the Licensed Compound, or the Licensed Product or relating to the transactions contemplated by this Agreement (including any claim alleging that the Exploitation of the Licensed Compound or Licensed Product in the Territory infringes or misappropriates any intellectual property rights of a Third Party);

14.2.4 all officers, employees and contractors of Akcea or its Affiliates that are inventors of any of the inventions claimed in the Akcea Patent Rights or that have performed Development, Manufacturing or other Exploitation activities on behalf of Akcea or its Affiliates, as applicable, have entered into written agreements pursuant to which such Persons are obligated to assign all rights, title, and interests in and to any such inventions developed by them, whether or not patentable, to Akcea or such Affiliate, respectively, as the sole owner thereof;

14.2.5 to Akcea's Knowledge, no officer, employee or contractor of Akcea or its Affiliates is, or during the Term will be, subject to any agreement that requires such individual to assign any interest in any Licensed Technology to any Third Party;

14.2.6 there are no additional licenses or rights (beyond those granted to AstraZeneca under this Agreement) under any intellectual property owned or Controlled by Akcea that would be required in order for AstraZeneca to Exploit the Licensed Compound and the Licensed Product that is being clinically Developed as of the Execution Date;

14.2.7 the Licensed Technology constitutes all of the Patent Rights and Know-How owned or otherwise Controlled by Akcea and its Affiliates that are necessary to Exploit the Licensed Compound and the Licensed Product that is being clinically Developed as of the Execution Date;

14.2.8 neither Akcea nor its Affiliates has previously assigned, transferred, conveyed, or otherwise encumbered its rights, title, or interests in or to the Licensed Technology in a manner that conflicts with any rights granted to AstraZeneca hereunder with respect to the Licensed Compound or the Licensed Product;

14.2.9 other than the PTC Agreement, the Prior Agreements and the Permitted Licenses, neither Akcea nor any of its Affiliates is a party to any agreement with a Third Party that limits any of the rights and licenses that would be granted to AstraZeneca under this Agreement absent such agreement;

14.2.10 (a) Schedule 1.11 (Akcea Core Technology Patent Rights), Schedule 1.18 (Akcea Manufacturing Patent Rights) and Schedule 1.23 (Akcea Product-Specific Patent Rights) set forth true, correct, and complete lists of all Patent Rights owned, licensed or otherwise Controlled by Akcea or any of its Affiliates that relate to the Licensed Compound or the Licensed Product, (b) except as otherwise indicated in Schedule 1.11 (Akcea Core Technology Patent Rights), Schedule 1.18 (Akcea Manufacturing Patent Rights) or Schedule 1.23 (Akcea Product-Specific Patent Rights), each issued Akcea Patent Right is in full force and effect and each issued or pending Akcea Patent Right has been filed and prosecuted in good faith, and (c) Akcea or its Affiliates have timely paid all application, registration, maintenance and renewal fees payable with respect to such Patent Rights that are pending or granted and all necessary documents and certificates have been filed with the relevant agencies for the purpose of maintaining such Patent Rights;

14.2.11 to Akcea's Knowledge, no Third Party (a) is infringing, misappropriating or violating any Akcea Core Technology Patent Rights or Akcea Manufacturing Patent Rights (and there is no claim by Akcea that a Third Party is or was infringing, misappropriating or violating any Akcea Core Technology Patent Rights or Akcea Manufacturing Patent Rights) or misappropriating any Know-How included in the Akcea Core Technology IP or Akcea Manufacturing IP, in each case, with respect to a Competitive Oligo, (b) is infringing, misappropriating or violating any Akcea Product-Specific Patent Rights (and there is no claim by Akcea that a Third Party is or was infringing, misappropriating or violating any Akcea Product-Specific Patent Rights) or misappropriating any Know-How included in the Akcea Product-Specific IP, and (c) has challenged or threatened to challenge the inventorship, ownership, Akcea's right to use, scope, validity or enforceability of any Akcea Patent Rights (including, by way of example, through the institution or written threat of institution of interferences, derivation, post-grant review, opposition, nullity, reexamination, reissue, revocation, *inter partes* or similar invalidity proceedings before the United States Patent and Trademark Office or any analogous foreign Governmental Authority);

14.2.12 Akcea has set forth on Schedule 1.94 (Existing In-License Agreements) a true, correct, and complete list of all agreements pursuant to which a Third Party has granted Akcea or its Affiliates a license under any Know-How or Patent Rights that are necessary to Exploit the Licensed Compound or the Licensed Product, and all such Patent Rights and Know-How are included in the Licensed Technology. All Existing In-License Agreements are in full force and effect, and Akcea has provided AstraZeneca with true and complete copies of each such Existing In-License Agreement and all amendments thereto. Neither Akcea, its Affiliates nor, to Akcea's Knowledge, the counterparty to an Existing In-License Agreement is in default with respect to a material obligation under such Existing In-License Agreement, and none of such parties has claimed or, to Akcea's Knowledge, has grounds upon which to claim that the other party is in default with respect to a material obligation under any Existing In-License Agreement;

14.2.13 neither Akcea nor its Affiliates have received any written claim alleging, and do not have Knowledge of any claim or any fact or circumstance indicating, that Exploitation of the Licensed Compound and Licensed Product infringe any Patent Rights or misappropriate or otherwise violate other intellectual property rights of a Third Party;

14.2.14 no Licensed Technology has been created pursuant to, and is not subject to, any funding agreement with any government or Governmental Authority or any Third Party, and is not subject to the requirements of the Bayh-Dole Act or any similar provision of any applicable Law. No funding, facilities or personnel of any Governmental Authority were used, directly or indirectly, to develop or create, in whole or in part, any Licensed Technology;

14.2.15 to Akcea's Knowledge, no additional licenses or other intellectual property rights are required from any Third Party to conduct activities under the Development Plan and Budget as it exists on the Execution Date;

14.2.16 each Regulatory Filing filed by Akcea or its Affiliates with respect to the Licensed Compound or the Licensed Product prior to the Execution Date and the Closing Date was true, complete and accurate in all material respects and timely filed;

14.2.17 any and all Regulatory Filings filed by Akcea or its Affiliates with respect to the Licensed Compound or the Licensed Product have been provided to AstraZeneca in an appropriate electronic format prior to the Execution Date. Neither Akcea nor its Affiliates or licensees has received any written notice or allegation from any Regulatory Authority regarding (a) any actual, alleged, possible, or potential violation of or failure to comply with any Law with respect to Regulatory Filings for the Licensed Product, or (b) any actual, proposed, or potential revocation, withdrawal, suspension, cancellation, termination, or modification of any Regulatory Filing for the Licensed Product, and, to Akcea's Knowledge, there is no reasonable basis for any such notice or allegation;

14.2.18 all preclinical and clinical investigations of the Licensed Product sponsored by Akcea or its Affiliates and all other Licensed Product Development activities of Akcea or its Affiliates have been and are being conducted in material compliance with applicable protocols, procedures, Laws, rules, regulations and guidances, including cGCP and applicable protocols, procedures, Laws, rules, regulations and guidances restricting the use and disclosure of individually identifiable health information. Neither Akcea nor its Affiliates has received any written notice from the FDA, the EMA or any other Regulatory Authority performing functions similar to those performed by those with respect to any ongoing clinical or pre-clinical studies or tests of the Licensed Product requiring the termination, suspension or material modification of such studies or tests, and no Governmental Authority has commenced any action to place a clinical hold order on, or otherwise terminate or suspend, any ongoing Clinical Trial of the Licensed Product conducted by or on behalf of Akcea or its Affiliates;

14.2.19 all inventory of any API, drug product and packaged Clinical Trial material for the Licensed Product transferred from Akcea to AstraZeneca hereunder (a) meets and was Manufactured in accordance with all specifications and all applicable Laws and other regulatory requirements (including cGMP where applicable), (b) is free from contamination, diluents and defects in materials and workmanship, and (c) is not adulterated or misbranded;

14.2.20 to Akcea's Knowledge, neither Akcea nor any of its Affiliates has committed any act, or omitted to commit any act, that may cause the Akcea Patent Rights to expire prematurely or be declared invalid or unenforceable;

14.2.21 to Akcea's Knowledge, true, complete and correct copies of all material information with respect to the safety and efficacy of the Licensed Compound and the Licensed Product that are not otherwise publicly available have been provided to AstraZeneca;

14.2.22 to Akcea's Knowledge, there is no material omission from, or material misrepresentation in, [***] as of the Execution Date;

14.2.23 neither Akcea nor any of its Affiliates has provided the Licensed Compound or the Licensed Product to a Third Party under the Prior Agreements or the Existing In-License Agreements;

14.2.24 no consents from the Inbound Licensors under the In-License Agreements are required to enter into this Agreement and to grant the licenses to AstraZeneca hereunder, other than the consent from Ionis contained in that certain Letter Agreement by and among AstraZeneca, Akcea and Ionis, dated as of the Execution Date; and

14.2.25 neither Akcea nor its Affiliates has, regarding or related to the Licensed Compound, the Licensed Product or the Akcea Product-Specific IP, been subject to a corporate integrity agreement, deferred prosecution agreement, consent decree, monitoring agreement, settlement agreement or other similar agreement or Order mandating or prohibiting future or past activities.

14.3 **Covenants of the Parties**. From and after the Execution Date through the expiration or earlier termination of this Agreement, each Party covenants to the other Party as follows:

14.3.1 such Party will not, during the Term, employ or use the services of any Person that is debarred, in connection with the Exploitation of the Licensed Products. If such Party becomes aware of the debarment or threatened debarment of any Person providing services to such Party that are directly or indirectly related to activities under this Agreement, including such Party itself or its Affiliates or Sublicensees, such Party will promptly notify the other Party in writing;

14.3.2 during the Term, such Party will take reasonable precautions to preserve the confidentiality of the Know-How contained in the Licensed Technology, subject to Article 13 (including authorized disclosures in Section 13.3) (with, for the purposes of this Section 14.3.2, the exceptions to confidentiality available for a Receiving Party also applying to Akcea *mutatis mutandis)*;

14.3.3 (a) Akcea shall not, and shall cause its Affiliates not to, incur or permit to exist, with respect to any Licensed Technology, and (b) AstraZeneca shall not, and shall cause its Affiliates not to, incur or permit to exist, with respect to any AstraZeneca IP, in each case ((a) and (b)), any lien, encumbrance, charge, security interest, mortgage, liability, assignment, grant of license or other obligation that is or would be inconsistent with the licenses and other rights granted to the other Party under this Agreement.

14.4 **Covenants of Akcea**. From and after the Execution Date through the expiration or earlier termination of this Agreement, Akcea covenants to AstraZeneca as follows:

14.4.1 Akcea will not enter into any agreement or other obligation with any Third Party, or amend an existing agreement with a Third Party, in each case, that would have an adverse effect on Akcea's ability to grant the licenses (or sublicenses as the case may be) granted to AstraZeneca, or perform its obligations, under this Agreement; and

14.4.2 with respect to any changes resulting from Akcea's obligations under the last sentence of Section 12.2.1(a) and otherwise upon AstraZeneca's reasonable written request (such request not to be submitted to Akcea more than once every Calendar Year), Akcea will promptly update Schedule 1.11 (Akcea Core Technology Patent Rights), Schedule 1.18 (Akcea Manufacturing Patent Rights) and Schedule 1.23 (Akcea Product-Specific Patent Rights), and submit such amended Schedules to AstraZeneca;

14.4.3 Akcea and its Affiliates, as applicable, will at all times have obtained the necessary consents from the Inbound Licensors under the In-License Agreements to enter into this Agreement and to grant the licenses to AstraZeneca hereunder, and, upon AstraZeneca's written request, will provide to AstraZeneca written evidence of same;

14.4.4 neither Akcea nor its Affiliates will amend, modify, terminate, or waive any rights under any In-License Agreement, Prior Agreement or any agreement with an Authorized CMO listed on Schedule 8.3.2, in each case, in a manner that would adversely affect AstraZeneca's rights or obligations under this Agreement without AstraZeneca's prior written consent;

14.4.5 neither Akcea nor its Affiliates will commit any acts or permit the occurrence of any omissions that would cause or result in the termination of any In-License Agreement or any agreement with an Authorized CMO listed on Schedule 8.3.2 that is Manufacturing the API or drug product or Licensed Product being used to conduct the ongoing Phase 3 Clinical Trials as of the Execution Date, which termination would adversely affect AstraZeneca's rights or obligations under this Agreement, without AstraZeneca's prior written consent. Akcea or Ionis, as applicable, will notify AstraZeneca in writing within [***] after any such termination of any such agreement;

14.4.6 Akcea or its Affiliates shall be and remain solely responsible for fulfilling and performing at its cost and expense, any and all obligations under each In-License Agreement, each Prior Agreement, and each agreement with an Authorized CMO listed on Schedule 8.3.2, including timely, full and complete payment of any and all amounts due thereunder or in connection therewith to the other parties thereto, and will otherwise remain, and cause its Affiliates to otherwise remain, in compliance in all material respects with all such agreements;

14.4.7 Akcea will furnish AstraZeneca with copies of all notices received by Akcea or any of its Affiliates relating to any alleged breach or default by Akcea or any of its Affiliates under any In-License Agreement, Prior Agreement or agreement with an Authorized CMO listed on Schedule 8.3.2, in each case, that would reasonably be expected to adversely affect AstraZeneca's rights hereunder, promptly after receipt thereof and thereafter furnish AstraZeneca with copies of all correspondence and summaries of material discussions between the applicable parties to the In-License Agreement or Prior Agreement relating to the alleged breach, including any proposed resolution of the matter; and

14.4.8 Akcea will promptly furnish AstraZeneca with true and complete copies of all Future In-License Agreements and all amendments to the In-License Agreements and Prior Agreements arising after the Execution Date.

14.5 **Disclaimer**. EXCEPT AS OTHERWISE EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY THAT ANY PATENTS ARE VALID OR ENFORCEABLE, AND EXPRESSLY DISCLAIMS ALL IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE AND NON-INFRINGEMENT. BOTH PARTIES HEREBY ACKNOWLEDGE AND AGREE THAT THE OTHER PARTY MAKES (AND HAS MADE) NO REPRESENTATION OR WARRANTY, EITHER EXPRESS OR IMPLIED, AT LAW OR IN EQUITY, THAT THE COMPOUND OR PRODUCT WILL BE SUCCESSFUL, THAT IT WILL BE ABLE TO SUCCESSFULLY ACHIEVE THE MILESTONE EVENTS SET FORTH IN ARTICLE 11 OR THAT IT WILL BE ABLE TO ACHIEVE ANY AMOUNT OF NET SALES, AND EACH PARTY SPECIFICALLY DISCLAIMS THAT IT IS RELYING UPON OR HAS RELIED UPON ANY SUCH REPRESENTATIONS OR WARRANTIES THAT MAY HAVE BEEN MADE BY ANY PERSON.

ARTICLE 15
INDEMNIFICATION; INSURANCE

15.1 **Indemnification by AstraZeneca**. AstraZeneca will defend, and indemnify and hold harmless, Akcea and its Affiliates and its and their respective directors, officers, employees, agents, representatives, successors and assigns (collectively, the "***Akcea Indemnified Parties***"), from and against any and all liabilities, damages, losses, costs and expenses, including interest penalties and reasonable attorneys' fees and expenses (collectively, "***Losses***"), to the extent arising out of or resulting from any Third Party suits, claims, actions, proceedings or demands ("***Third Party Claims***") to the extent based upon:

15.1.1 any breach of any representation, warranty or covenant made by AstraZeneca in this Agreement;

15.1.2 the Exploitation of the Licensed Compound or Licensed Product by AstraZeneca or its Affiliates or its or their Sublicensees or subcontractors, other than Losses shared pursuant to Section 15.3; or

15.1.3 the gross negligence or willful misconduct of AstraZeneca or any of the AstraZeneca Indemnified Parties in the exercise of their rights or performance of their obligations hereunder;

provided that, in the case of each of Sections 15.1.1 through 15.1.3 above, AstraZeneca will not be obligated to so defend, and indemnify and hold harmless, the Akcea Indemnified Parties for any Third Party Claim to the extent that such Third Party Claim is based upon an action or omission for which Akcea would have an obligation to indemnify the AstraZeneca Indemnified Parties under Section 15.2.1, Section 15.2.2 or Section 15.2.4 if such Loss were incurred by an AstraZeneca Indemnified Party.

15.2 **Indemnification by Akcea**. Akcea will defend, and indemnify and hold harmless, AstraZeneca and its Affiliates and its and their Sublicensees and its and their respective directors, officers, employees, agents, representatives, successors and assigns (collectively, the "***AstraZeneca Indemnified Parties***"), from and against any and all Losses, to the extent arising out of or resulting from any Third Party Claims to the extent based upon:

15.2.1 any breach of any representation, warranty or covenant made by Akcea in this Agreement;

15.2.2 the Exploitation of the Licensed Compound or Licensed Product by Akcea or its Affiliates or subcontractors prior to the Closing Date;

15.2.3 the Exploitation, including the Co-Commercialization and Medical Affairs Activities (if any), of the Licensed Compound or Licensed Product by Akcea or its Affiliates or subcontractors during the Term and after termination of this Agreement, other than Losses shared pursuant to Section 15.3; or

15.2.4 the gross negligence or willful misconduct of Akcea or any of the Akcea Indemnified Parties in the exercise of their rights or performance of their obligations hereunder;

provided that, in the case of each of Sections 15.2.1 through 15.2.4 above, Akcea will not be obligated to so defend, and indemnify and hold harmless, the AstraZeneca Indemnified Parties for any Third Party Claim to the extent that such Third Party Claim is based upon an action or omission for which AstraZeneca would have an obligation to indemnify the Akcea Indemnified Parties under Section 15.1.1 or Section 15.1.3 if such Loss were incurred by an Akcea Indemnified Party.

15.3 **Losses in the U.S**. All Losses incurred by either Party arising from any Third Party Claim relating to the Exploitation of a Licensed Product in the U.S. after the Closing Date and prior to the Opt-Out Date (if any) during the Term will be shared by the Parties as an Other Operating Expense in accordance with Section 11.10, *provided* that such Other Operating Expenses will not include Losses of a Party or its Affiliate to the extent such Losses are: (a) caused by a breach of this Agreement by a Party or Affiliate; or (b) caused by the gross negligence or willful misconduct of a Party or its Affiliate, and any such Losses described in clause (a) or (b) will not be shared by the Parties. If either Party learns of any Third Party Claim with respect to Losses covered by this Section 15.3, such Party shall provide the other Party with prompt written notice thereof. The Parties shall confer with respect to how to respond to such Third Party Claim and how to handle such Third Party Claim in an efficient manner. In the absence of such an agreement, each Party shall have the right to take such action as it deems appropriate.

15.4 **Procedure**.

15.4.1 **Notice of Claim**. All indemnification claims provided for in Section 15.1 and Section 15.2 will be made solely by such Party to this Agreement (the "***Indemnified Party***"). The Indemnified Party will give the indemnifying Party prompt written notice (an "***Indemnification Claim Notice***") of any Losses or the discovery of any fact upon which the Indemnified Party intends to base a request for indemnification under Section 15.1 or Section 15.2, but in no event will the indemnifying Party be liable for any Losses to the extent such Losses result from any delay in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Loss (to the extent that the nature and amount of such Loss is known at such time). The Indemnified Party will furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of any Losses and Third Party Claims.

15.4.2 Control of Defense. At its option, the indemnifying Party may assume the defense of any Third Party Claim by giving written notice to the Indemnified Party within [***] after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption of the defense of a Third Party Claim by the indemnifying Party will not be construed as an acknowledgment that the indemnifying Party is liable to indemnify the Indemnified Party in respect of the Third Party Claim, nor will it constitute a waiver by the indemnifying Party of any defenses it may assert against the Indemnified Party's claim for indemnification. Upon assuming the defense of a Third Party Claim, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party. In the event the indemnifying Party assumes the defense of a Third Party Claim, the Indemnified Party will as soon as is reasonably possible deliver to the indemnifying Party all original notices and documents (including court papers) received by the Indemnified Party in connection with the Third Party Claim. Should the indemnifying Party assume the defense of a Third Party Claim, except as provided in this Section 15.4.2, the Indemnified Party will be responsible for the legal costs or expenses subsequently incurred by such Indemnified Party in connection with the analysis, defense or settlement of the Third Party Claim.

15.4.3 Right to Participate in Defense. Without limiting Section 15.4.2, any Indemnified Party will be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided*, *however*, that such employment will be at the Indemnified Party's own cost and expense unless (a) the employment thereof has been specifically authorized by the indemnifying Party in writing, (b) the indemnifying Party has failed to assume the defense and employ counsel in accordance with Section 15.4.2 (in which case the Indemnified Party will control the defense), or (c) the interests of the Indemnified Party and the indemnifying Party with respect to such Third Party Claim are sufficiently adverse to prohibit the representation by the same counsel of both Parties under applicable Law, ethical rules or equitable principles in which case the indemnifying Party will be responsible for any such costs and expenses of counsel for the Indemnified Party.

15.4.4 Settlement. With respect to any Third Party Claims relating solely to the payment of money damages in connection with a Third Party Claim and that will not admit liability or violation of Law on the part of the Indemnified Party or result in the Indemnified Party's becoming subject to injunctive or other relief or otherwise adversely affecting the business of the Indemnified Party in any manner (such as granting a license or admitting the invalidity of a Patent Right Controlled by an Indemnified Party), and as to which the indemnifying Party will have acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party will have the sole right to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss, on such terms as the indemnifying Party, in its sole discretion, will deem appropriate. With respect to all other Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with Section 15.4.2, the indemnifying Party will have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Loss provided it obtains the prior written consent of the Indemnified Party (which consent will not be unreasonably withheld, conditioned or delayed). The indemnifying Party will not be liable for any settlement, consent to entry of judgment, or other disposition of a Loss by an Indemnified Party that is reached without the written consent of the indemnifying Party. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnified Party will admit any liability with respect to or settle, compromise or discharge, any Third Party Claim without the prior written consent of the indemnifying Party, such consent not to be unreasonably withheld, conditioned or delayed.

15.4.5 **Cooperation**. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, the Indemnified Party will, and will cause each other Indemnified Party to, cooperate in the defense or prosecution thereof and will furnish such records, information and testimony, provide such witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation will include affording to the indemnifying Party access during normal business hours to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Third Party Claim, and making Indemnified Parties and other employees and agents available on a mutually convenient basis to provide additional information and explanation of any material provided hereunder, and the indemnifying Party will reimburse the Indemnified Party for all its reasonable Out-Of-Pocket Costs in connection therewith.

15.4.6 **Costs and Expenses**. Except as provided above in this Section 15.4, the costs and expenses, including attorneys' fees and expenses, incurred by the Indemnified Party in connection with any claim will be reimbursed [***] by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

15.5 **Insurance**. Each Party will maintain with insurers with a minimum "A-" AM Best rating, at its own cost, reasonable insurance against liability and other risks associated with its activities and obligations under this Agreement, including its Development, Manufacturing, Commercialization and other Exploitation activities, as applicable, and its indemnification obligations hereunder, in such amounts (subject to such deductibles, which are the sole responsibility of the named insured) and on such terms as are reasonable and customary for prudent practices for a company of similar size and of similar resources as such Party for the activities to be conducted by it under this Agreement. Each Party will promptly furnish to the other Party evidence of such insurance prior to the Closing Date and annually thereafter. Each Party will provide a minimum of [***] written notice of any cancellation, with no replacement policy, to the other Party. All insurance of a Party will be primary and non-contributing to any insurance carried by the other Party, to the extent of the first Party's indemnification obligations. Notwithstanding the foregoing, AstraZeneca may self-insure, in whole or in part, the insurance requirements described in this Section 15.5.

15.6 **Damages Waiver**. EXCEPT FOR (A) CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 15 OR SECTION 11.13.3. (B) CLAIMS ARISING OUT OF A PARTY'S WILLFUL MISCONDUCT, (C) A PARTY'S BREACH OF SECTION 9.2 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 16
TERM AND TERMINATION

16.1 **Term**. The term of this Agreement will commence as of the Closing Date and, unless terminated earlier, shall (a) with respect to the ROW Territory, on a Licensed Product-by-Licensed Product and country-by-country basis, continue until the expiration of the Royalty Term for such Licensed Product in such country and (b) with respect to the U.S., (i) if Akcea does not exercise its Opt-Out Right, until the Parties (and their Affiliates and its and their sublicensees) cease all Development, Commercialization and Medical Affairs activities for the Licensed Product in the U.S. and (ii) if Akcea exercises its Opt-Out Right, until expiration of the Royalty Term for such Licensed Product in the U.S. (the "***Term***"). If the Closing Date has not occurred by the [***] following the Execution Date, then this Agreement may be terminated by either Party upon written notice to the other Party, *provided* that a Party shall not be entitled to terminate this Agreement pursuant to this sentence if such Party is in breach of this Agreement and such breach has caused the Closing Date to not occur by such date.

16.2 **Termination**.

16.2.1 **Termination for Material Breach**.

(a) If a Party (the "***Breaching Party***") materially breaches this Agreement (including any material breach of such Party's diligence obligations pursuant to Section 2.1 or Section 3.1.1, as applicable), in addition to any other right and remedy the other Party (the "***Non-Breaching Party***") may have, the Non-Breaching Party may terminate this Agreement in its entirety upon written notice to the Breaching Party if the Breaching Party, after receiving written notice identifying such material breach in reasonable detail (a "***Default Notice***"), fails to cure such material breach within [***] after delivery of the Default Notice (or within [***] after delivery of the Default Notice if such material breach is solely based on the Breaching Party's failure to pay any amounts due hereunder) (such [***] or [***] period, as applicable, the "***Cure Period***"); *provided* that (i) if such breach (other than a payment breach) cannot be cured within the Cure Period, if the Breaching Party commences actions to cure such breach within the Cure Period and thereafter diligently continues such actions, then the termination shall not become effective unless and until the Breaching Party fails to diligently continue such actions, and (ii) with respect to any alleged breach by the Breaching Party of its diligence obligations set forth in Section 2.1 or Section 3.1.1, as applicable, the Non-Breaching Party shall first provide written notice thereof to the Breaching Party, and the Parties shall 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 for not less than [***] (or such longer period as may be mutually agreed by the Parties) before the Non-Breaching Party may issue any Default Notice with respect to such alleged breach (for clarity, the Cure Period shall not commence prior to the conclusion of such good faith discussions and the subsequent issuance of a Default Notice by Non-Breaching Party).

(b) Notwithstanding Section 16.2.1(a), if the material breach and failure to cure contemplated in Section 16.2.1(a) is with respect to AstraZeneca's diligence obligations under Section 2.1 or Section 3.1.1 with respect to the Development or Commercialization of a Licensed Product, but does not affect, and is not reasonably likely to affect, [***], Akcea shall not have the right to terminate this Agreement in its entirety, but shall have the right to terminate this Agreement solely with respect to [***] that are affected by, or reasonably likely to be affected by, such material breach, and this Agreement shall remain in full force and effect with respect to [***] that are not affected, or not reasonably likely to be affected.

(c) **Disputes Regarding Material Breach**. Notwithstanding the foregoing, if the Breaching Party disputes in good faith the existence, materiality or failure to cure of any alleged uncured material breach, and provides notice to the Non-Breaching Party of such dispute within the relevant Cure Period, then the Non-Breaching Party will not have the right to terminate this Agreement in accordance with Section 16.2.1, unless and until (i) it has been determined in accordance with Section 17.1 that this Agreement was materially breached by the Breaching Party and (ii) the Breaching Party fails to cure such material breach within [***] after 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.

16.2.2 AstraZeneca's Termination for Convenience. At any time following payment by AstraZeneca of the upfront fees under Section 11.1, AstraZeneca will be entitled to terminate this Agreement, on a region-by-region basis, for convenience by providing [***] written notice to Akcea of such termination. For purposes of this Section 16.2.2, "region" shall mean each of the U.S. and the ROW Territory.

16.2.3 Termination for Patent Challenge. If AstraZeneca or any of its Affiliates (a) commences or actively, directly and voluntarily participates in any action or proceeding (including any patent opposition or re-examination proceeding), or otherwise asserts any claim, challenging or denying the validity or enforceability of any claim of any Akcea Patent Right that is licensed to AstraZeneca under this Agreement or (b) actively assists any other person or entity in bringing or prosecuting any action or proceeding (including any patent opposition or re-examination proceeding) challenging or denying the validity or enforceability of any claim of any such Akcea Patent Right (each of (a) and (b), a "***Patent Challenge***"), then, except as otherwise set forth in this Section 16.2.3, Akcea shall have the right, in its sole discretion, to give notice to AstraZeneca that Akcea may terminate this Agreement [***] following such notice, and, unless AstraZeneca and its Affiliates withdraw or cause to be withdrawn such Patent Challenge(s) (or in the case of *ex-parte* proceedings, multi-party proceedings, or other Patent Challenges that AstraZeneca or its Affiliate does not have the power to unilaterally withdraw or cause to be withdrawn, AstraZeneca and its Affiliates cease actively assisting any other party to such Patent Challenge and, to the extent AstraZeneca or any of its Affiliates is a party to such Patent Challenge, it withdraws from such Patent Challenge) within such [***] period, Akcea shall have the right to terminate this Agreement by providing written notice thereof to AstraZeneca, unless such termination is prohibited under applicable Law. Notwithstanding the foregoing, any participation by AstraZeneca or its Affiliates or its or their employees in any claim, challenge or proceeding (i) that has been compelled by a court, patent office, or Third Party (other than any Sublicensee) or as required under a pre-existing agreement between AstraZeneca's employee(s) or consultant(s) and their prior employer(s) or (ii) that is necessary or reasonably required to assert a cross-claim or a counterclaim or to respond to a court request or order or administrative law request or order, including asserting any defense or counterclaim in, or otherwise responding to an action for infringement of intellectual property asserted, filed, or threatened to be filed, against AstraZeneca or its Affiliate by Akcea or any of its Affiliates or its (sub)licensees, in each case ((i) and (ii)), shall not constitute active and voluntary participation or active assistance and shall not give rise to Akcea's right to terminate this Agreement. In addition, Akcea shall not have the right to terminate this Agreement pursuant to this Section 16.2.3 if any Affiliate that first becomes an Affiliate of AstraZeneca after the Closing Date was undertaking activities in connection with a Patent Challenge prior to such Affiliate first becoming an Affiliate of AstraZeneca if such Affiliate withdraws or causes to be withdrawn such Patent Challenge (or in the case of *ex-parte* proceedings, multi-party proceedings, or other Patent Challenges that such Affiliate does not have the power to unilaterally withdraw or cause to be withdrawn, ceases actively assisting any other party to such Patent Challenge and, to the extent such Affiliate is a party to such Patent Challenge, withdraws from such Patent Challenge) within the earlier to occur of (A) [***] and (B) [***], and in all cases, *provided*, that neither AstraZeneca nor any AstraZeneca Affiliate thereafter continues such Patent Challenge or, knowingly, the provision of any active assistance to any person or entity in respect of the same. Each Sublicense shall contain a provision that is consistent with this Section 16.2.3 with respect to Patent Challenges by the applicable Sublicensee. If a Sublicensee commences or actively, directly and voluntarily participates in, or actively assists any other person or entity in bringing or prosecuting any Patent Challenge, and fails to withdraw or cause to be withdrawn or cease actively assisting any other party to such Patent Challenge in accordance with the requirements of this Section 16.2.3, then, subject to the exceptions set forth above (applied *mutatis mutandis* to Sublicensees), AstraZeneca shall terminate the applicable Sublicense and, *provided* that AstraZeneca timely terminates such Sublicense, Akcea shall not have a termination right under this Section 16.2.3 as a result of such Patent Challenge.

16.2.4 Termination for Insolvency. In the event that either Party (a) files for protection under bankruptcy or insolvency laws, (b) makes an assignment for the benefit of creditors, (c) appoints or suffers appointment of a receiver or trustee over substantially all of its property that is not discharged within [***] after such filing, (d) proposes a written agreement of composition or extension of its debts, (e) proposes or is a party to any dissolution or liquidation, (f) files a petition under any bankruptcy or insolvency act or has any such petition filed against it that is not discharged within [***] after the filing thereof or (g) admits in writing to its creditors its inability generally to meet its obligations as they fall due in the general course, then the other Party may terminate this Agreement in its entirety effective immediately upon written notice to such Party.

16.3 Effects of Termination.

16.3.1 In General. Without limiting any other legal or equitable remedies that either Party may have, if this Agreement is terminated in its entirety pursuant to Section 16.2, then the following will occur:

(a) except as required to perform activities under this Section 16.3, including the Transition Services, the license grants to AstraZeneca under Section 8.1 and to Akcea under Section 8.2 will terminate immediately and be of no further force or effect. Subject to Section 16.3.3 and except as required to perform activities under this Section 16.3, including the Transition Services, AstraZeneca shall, and, subject to Section 8.5, shall cause its Affiliates and its and their Sublicensees to, cease selling the Licensed Product.

(b) **Reversion License**.

(i) Except with respect to any termination by AstraZeneca pursuant to Section 16.2.1(a) or Section 16.2.4, upon Akcea's request, which request must be made no later than the later of (A) [***] after the effective date of termination and (B) [***] following written notice by AstraZeneca to Akcea asking Akcea to confirm if Akcea wishes to have AstraZeneca grant the Reversion License, subject to the remaining subsections of this Section 16.3.1(b), AstraZeneca agrees to grant and hereby grants to Akcea, effective as of the effective date of such termination, a perpetual, non-exclusive, royalty-bearing (solely as set forth in Section 16.3.1(b)(ii)) license under the AstraZeneca Reversion IP Controlled by AstraZeneca or any of its Affiliates as of the effective date of termination that is [***] as of the effective date of such termination for the Exploitation of the Licensed Product in the Field in the Terminated Territory to Exploit the Licensed Product in the Field in the Terminated Territory (the "***Reversion License***"). For clarity, the Reversion License will exclude any Know-How and Patent Rights that are related to or claim (1) [***] or (2) [***] as of the effective date of such termination to Exploit the Licensed Product as it is being Commercialized by AstraZeneca or its Affiliates in the applicable Terminated Territory as of the effective date of termination.

(ii) Without limiting Akcea's obligations in Section 16.3.1(b)(iii), the Reversion License shall be royalty-free if the Agreement is terminated by Akcea pursuant to Section 16.2.1 or Section 16.2.4. In all other events of termination, the Reversion License shall be royalty-bearing as follows: (A) if the effective date of the termination occurs prior to [***], then Akcea will pay AstraZeneca [***], or (B) if the effective date of termination occurs after [***], then Akcea will pay AstraZeneca [***]. The Reversion License will be granted on the effective date of termination regardless of if the Parties have reached agreement on the [***] terms of such Reversion License; *provided* that [***] will be due [***] as of the effective date of termination on the terms subsequently agreed to by the Parties. Once the Parties have reached agreement on such terms, Akcea will pay [***] from the effective date of termination through the date of such agreement within [***] after receipt of an invoice from AstraZeneca. For purposes of this Section 16.3.1(b), the definition of "Net Sales," shall apply *mutatis mutandis* to Akcea's obligations to pay royalties under this Section 16.3.1(b) as they apply to AstraZeneca and, solely for such purpose, each reference (and any related definitions) to (1) AstraZeneca shall be deemed to be a reference to Akcea, (2) Akcea shall be deemed to be a reference to AstraZeneca and (3) a Sublicensee shall be deemed to be a reference to a licensee or sublicensee of Akcea or its Affiliates.

(iii) To the extent that any AstraZeneca Reversion IP that is the subject of the Reversion License is in-licensed by AstraZeneca or any of its Affiliates, AstraZeneca shall provide a copy of such in-license or other agreement to Akcea (which copy may be redacted as necessary to comply with its obligations of confidentiality to the counterparty *provided* that such redactions do not undermine Akcea's ability to comply with such in-license or understand the [***] if it were to take a sublicense). Akcea will promptly notify AstraZeneca if the Reversion License should include such in-licensed AstraZeneca Reversion IP. If Akcea elects to take a sublicense under such in-license as part of the Reversion License, then (A) any license to Akcea under such AstraZeneca Reversion IP pursuant to the Reversion License shall be subject to the terms and conditions of such in-license, (B) Akcea shall (1) provide the necessary reporting information to AstraZeneca in sufficient time as reasonably requested by AstraZeneca to enable AstraZeneca to comply with its obligations under such in-license and AstraZeneca's obligation to [***] pursuant to clause (2), (2) [***] and (3) not, and shall cause its Affiliates and (sub)licensees not to, take or fail to take any action if doing so (or not doing so) would cause AstraZeneca to be in breach of such in-license to the extent that any applicable obligations have been disclosed to Akcea and (C) [***]. For any in-licensed AstraZeneca Reversion IP that is the subject to the Reversion License but is also applicable to other products, the Parties shall use good faith efforts to appropriately allocate any upfront fees or sales milestones to Akcea's or its Affiliate's or sublicensee's practice of such sublicensed intellectual property that is included in the Reversion License and such other products.

(iv) Except with respect to any termination by AstraZeneca pursuant to Section 16.2.1(a) or Section 16.2.4, upon Akcea's request, which request must be made no later than the later of (A) [***] and (B) [***], the Parties will negotiate in good faith and on commercially reasonable terms, a perpetual, non-exclusive license under the Know-How and Patents Controlled by AstraZeneca or any of its Affiliates (other than Joint Know-How and Joint Patents) as of the effective date of termination that are not included in the Reversion License and that are necessary to Exploit the Licensed Product in the Field in the Terminated Territory as such Licensed Product is being clinically Developed by AstraZeneca or its Affiliates in the applicable Terminated Territory as of the effective date of termination.

(c) Except with respect to any termination by AstraZeneca pursuant to Section 16.2.1(a) or Section 16.2.4, AstraZeneca and its Affiliates will (i) assign to Akcea, upon Akcea's request, any contracts (including Supply Agreements) that are solely related to the Licensed Product in the Terminated Territory and freely assignable by AstraZeneca or its Affiliates at [***] AstraZeneca or its Affiliates (or for which Akcea agrees to [***]), (ii) use commercially reasonable efforts to obtain the applicable counter-party's consent to assign any such contracts that are not freely assignable, (iii) to the extent any contracts (including Supply Agreements) related to the Licensed Product in the Terminated Territory are not assigned to Akcea because such contracts are either not solely related to the Licensed Product in the Terminated Territory or not freely assignable, facilitate the replication of such agreements between Akcea and such Third Party and (iv) supply Licensed Product to Akcea at [***] to ensure continuity of supply of Licensed Product to patients in the Terminated Territory until the earlier of (1) [***] and (2) the assignment or replication of all Supply Agreements related to the Licensed Product in the Terminated Territory pursuant to this Section 16.3.1(c), or Akcea otherwise entering into supply agreement(s) with Third Parties sufficient to ensure such continuity of supply;

(d) AstraZeneca will provide to Akcea a detailed, fair and accurate description of the status of the Exploitation of the Licensed Product in each country in the Terminated Territory through the effective date of termination; and

(e) AstraZeneca will, and will ensure that its Affiliates and its and their Sublicensees, execute all documents and take all such further actions as may be reasonably requested by Akcea in order to give effect to the foregoing clauses.

16.3.2 In One or More Countries. If this Agreement is terminated with respect to one (1) or more countries but not the entire Territory, then, except as set forth below, the provisions of Section 16.3.1 shall apply, but only with respect to such terminated country or countries (and such country(ies) will be the Terminated Territory for purposes of Section 16.3.1), and this Agreement shall continue with respect to the other countries in the Territory:

(a) Section 16.3.1(a) shall not apply, and the license grants to AstraZeneca under Section 8.1 shall automatically be deemed to be amended with respect to the Terminated Territory to be non-exclusive and to exclude the right to Commercialize the Licensed Product in the Field in such Terminated Territory and AstraZeneca shall retain a non-exclusive right to Develop and Manufacture Licensed Compounds and Licensed Products in the Terminated Territory solely for the purposes of supporting Regulatory Approval or Commercialization of the Licensed Products in the Territory.

(b) Notwithstanding the Reversion License in Section 16.3.1(b), AstraZeneca reserves the right under the AstraZeneca Reversion IP that is the subject of the Reversion License to Develop and Manufacture Licensed Compounds and Licensed Products in the Terminated Territory solely for the purposes of supporting Regulatory Approval or Commercialization of Licensed Products in the Territory.

(c) Promptly after termination of this Agreement with respect to a Licensed Product in the Terminated Territory, the Parties shall enter into an agreement regarding (i) the maintenance of the global safety database for Licensed Products, (ii) a process for the exchange of adverse event safety data in a mutually agreed format in order to monitor the safety of Licensed Products and to meet reporting requirements of any applicable Regulatory Authorities in the Territory and Terminated Territory, and (iii) coordination of the Development, Manufacture and Commercialization of the Licensed Products in the Terminated Territory, on the one hand, and the Development, Manufacture and Commercialization of the Licensed Products in and for the Territory, on the other hand, as needed.

(d) AstraZeneca shall not, and shall not permit any of its Affiliates, and shall use commercially reasonable efforts not to permit any of its and their Sublicensees or distributors to, distribute, market, promote, offer for sale or sell any Licensed Products directly or indirectly (i) to any Person for use in the applicable Terminated Territory or (ii) to any Person in the Territory that AstraZeneca or any of its Affiliates or any of its or their Sublicensees or distributors knows is likely to distribute, market, promote, offer for sale or sell such Licensed Product for use in the applicable Terminated Territory or assist another Person to do so; *provided* that if such Terminated Territory includes a country where passive sales cannot be prohibited under applicable Law, then AstraZeneca, its Affiliates and its and their Sublicensees and distributors may, to the extent passive sales cannot be prohibited under applicable Law and such passive sales are made in accordance with applicable Law, passively sell any Licensed Product into other jurisdictions that are in the Terminated Territory, but may not actively sell or promote any Licensed Product in such Terminated Territory. If AstraZeneca or any of its Affiliates receives or becomes aware of the receipt by a Sublicensee or distributor of any orders for any Licensed Product for use in such Terminated Territory, then AstraZeneca or its Affiliates, as applicable, shall use good faith efforts to refer (or instruct its Sublicensee or distributor, as applicable, to refer) such orders to Akcea. AstraZeneca shall cause its Affiliates and its and their Sublicensees and distributors to notify Akcea of any receipt of any orders for Licensed Product for use in such Terminated Territory.

(e) Akcea shall not, and shall not permit any of its Affiliates, and shall use commercially reasonable efforts not to permit any of its and their (sub)licensees, or distributors to, distribute, market, promote, offer for sale or sell any Licensed Product directly or indirectly (i) to any Person for use in the Territory or (ii) to any Person in such Terminated Territory that Akcea or any of its Affiliates or any of its or their (sub)licensees or distributors knows is likely to distribute, market, promote, offer for sale or sell such Licensed Product for use in the Territory or assist another Person to do so; *provided* that if such Terminated Territory includes a country where passive sales cannot be prohibited under applicable Law, then Akcea, its Affiliates and its and their (sub)licensees and distributors may, to the extent passive sales cannot be prohibited under applicable Law and such passive sales are made in accordance with applicable Law, passively sell any Licensed Product into other jurisdictions that are in the Territory, but may not actively sell or promote any Licensed Product in the Territory. If Akcea or any of its Affiliates receives or becomes aware of the receipt by a (sub)licensee or distributor of any orders for any Licensed Product for use in the Territory, then Akcea or its Affiliates, as applicable, shall use good faith efforts to refer (or instruct its (sub)licensee or distributor, as applicable, to refer) such orders to AstraZeneca. Akcea shall cause its Affiliates and its and their (sub)licensees and distributors to notify AstraZeneca of any receipt of any orders for any Licensed Product for use in the Territory.

16.3.3 **Transition Services**. Except with respect to any termination by AstraZeneca pursuant to Section 16.2.1(a) or Section 16.2.4:

(a) **Transition Plan**.

(i) In addition to the effects set forth in Section 16.3.1 and Section 16.3.2, at Akcea's reasonable request and at Akcea's cost and expense, if this Agreement is terminated pursuant to Section 16.2, then AstraZeneca will use Commercially Reasonable Efforts to perform the Transition Services (as defined below) in accordance with the Transition Plan as set forth in this Section 16.3.3. Upon Akcea's request, the Parties will agree to a transition plan pursuant to Section 16.3.3(a)(ii) that includes all activities that are necessary to (A) if a Licensed Product is being Commercialized in the Terminated Territory, provide patients with continued access to the Licensed Product, (B) transition the responsibilities under all Regulatory Approvals and ongoing Clinical Trials for the Licensed Product in the Terminated Territory to Akcea or its designee and (C) transition the then-current supply process for the Licensed Product in the Terminated Territory to Akcea or its designee, in each case, as necessary for Akcea to Exploit the Licensed Product in the Terminated Territory as such Licensed Product is being clinically Developed or Commercialized by AstraZeneca or its Affiliates in the Terminated Territory as of the effective date of termination (collectively, the "***Transition Services***"), which plan, in addition to standard contractual provisions, will also address customer and commercial matters, adverse event reporting, Licensed Product complaints, reimbursement support and other patient contact center activities, Medical Affairs, government and managed care contracts, Manufacturing, quality, regulatory, pharmacovigilance/global safety database and post-approval studies and commitments (such plan, the "***Transition Plan***"). The Transition Plan shall also (x) set forth responsibility for all monitoring and follow up with respect to subjects/patients that were administered Licensed Products from and after the effective date of termination and (y) provide that at Akcea's election (1) AstraZeneca shall have the right for [***] after the effective date of such termination with respect to the Terminated Territory to sell or otherwise dispose of all Licensed Compounds and Licensed Products then in its inventory and any in-progress inventory, in each case that is intended for sale or disposition in the Terminated Territory, (2) Akcea shall purchase all such inventory and any in-progress inventory from AstraZeneca at [***], or (3) a combination of both (1) and (2), in each case to the extent practicable.

(ii) Akcea may elect to have AstraZeneca perform the Transition Services by providing written notice to AstraZeneca no later than the later of (A) [***] following the effective date of the termination and (B) [***] following written notice by AstraZeneca to Akcea asking Akcea to confirm if Akcea wishes to have AstraZeneca perform the Transition Services. If Akcea requests Transition Services, then Akcea shall propose a Transition Plan setting forth the Transition Services to be performed by AstraZeneca, including delivery and transition dates, and, for a period of [***] after such request, the Parties will use good faith efforts to negotiate a mutually agreeable version of such Transition Plan. If the Parties have not reached agreement on the Transition Plan within [***] after Akcea requests Transition Services, then either Party may refer such matter for resolution pursuant to Schedule 16.3.3(a)(ii). If Akcea elects to have AstraZeneca perform the Transition Services but the Parties have not reached agreement on the Transition Plan before the effective date of termination, then AstraZeneca will use Commercially Reasonable Efforts to maintain access to the Licensed Product in the Territory for patients that were receiving such Licensed Product through clinical Development or Commercialization as of the effective date of termination until such Transition Plan is either agreed upon by the Parties or resolved pursuant to Schedule 16.3.3(a)(ii). In addition, the Parties will, within [***] 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 Licensed 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 AstraZeneca is providing Transition Services, AstraZeneca and Akcea will mutually agree in writing on talking points and a communication plan to customers, specialty pharmacies, physicians, Regulatory Authorities, patient advocacy groups and clinical study investigators, and AstraZeneca will make all such communication to such entities in accordance with the mutually agreed talking points.

(iii) AstraZeneca will use Commercially Reasonable Efforts to perform the Transition Services in accordance with the Transition Plan for a period not to exceed [***] from the effective date of termination (the "***Transition Period***"); *provided* that if the Transition Plan is determined pursuant to the arbitration process set forth on Schedule 16.3.3(a)(ii) and the arbitrators select Akcea's Arbitration Proposal, then the Transition Period will be extended by the amount of time that elapsed from the time that the determination of the Transition Plan was referred for resolution pursuant to Schedule 16.3.3(a)(ii) until the arbitrators selected Akcea's Arbitration Proposal. AstraZeneca and Akcea may also mutually agree to extend the Transition Period.

(b) **Costs of Transition Services**. Akcea will pay [***] to perform the Transition Services. Unless otherwise agreed as part of the Transition Plan and subject to the terms and conditions of such Transition Plan, Akcea will own all Net Revenue (as defined in the Transition Plan) derived from the Licensed Product after the effective date of termination and AstraZeneca will remit all such Net Revenues to Akcea in accordance with the Transition Plan.

(c) **Responsibility for Transition Services**. Akcea or its designee will be sufficiently prepared to, and will, accept the transition of Development, Manufacturing and Commercialization activities with respect to the Licensed Product to Akcea or such designee on the timelines set forth in the agreed transition plan for the Transition Services. As between AstraZeneca and Akcea, AstraZeneca will have no liability under this Agreement with respect to a failure of, or delay in, the Transition Services to the extent AstraZeneca uses Commercially Reasonable Efforts to perform, and complies with applicable Law in performing, the Transition Services or to the extent caused by factors beyond AstraZeneca's reasonable control (including any failure or delay by Akcea or its designee in accepting the transition of Development, Manufacturing and Commercialization activities with respect to the Licensed Product in the Terminated Territory). If AstraZeneca encounters any delays, then the Parties shall discuss in good faith and agree upon extended timelines for completion of the Transition Services.

16.3.4 Additional Remedies of AstraZeneca in Lieu of Termination of this Agreement. If AstraZeneca has the right to terminate this Agreement in its entirety pursuant to Section 16.2.1(a) (after giving effect to the applicable Cure Period) or Section 16.2.4, then in lieu of AstraZeneca terminating pursuant to Section 16.2.1(a) or Section 16.2.4, as applicable, AstraZeneca shall have the right, as its sole and exclusive remedy for the events giving rise to AstraZeneca's termination right, to elect, by providing written notice to Akcea, to have this Agreement continue in full force and effect as modified by this Section 16.3.4, in which case, such modifications shall be effective as of the date AstraZeneca delivers such notice to Akcea:

(a) all rights and licenses granted to AstraZeneca under Section 8.1 shall become perpetual and irrevocable;

(b) AstraZeneca's obligations to pay milestones and royalties under Section 3.6.2(b)(i), Section 11.2, Section 11.3, Section 11.5 and Section 11.6 shall be reduced to [***]% of the amount that would otherwise have been payable under this Agreement;

(c) If Akcea has not exercised the Opt-Out Right, notwithstanding the expiration of the Second Opt-Out Period (if applicable), Akcea will be deemed to have exercised the Opt-Out Right, and the consequences thereof shall apply, subject to Section 16.3.4(b) and except that AstraZeneca will have no obligation to reimburse Akcea for [***]; and

(d) all other provisions would remain in full force and effect without change.

16.4 Accrued Rights; Surviving Provisions of the Agreement.

16.4.1 Subject to Section 16.2.1, termination or expiration of this Agreement (either in its entirety or with respect to one or more countries) for any reason will be without prejudice to any rights that will have accrued to the benefit of any Party prior to such termination or expiration, including any payment obligations accrued as of the date of such termination under Article 11 hereof, and any and all damages or remedies arising from any breach hereunder. Such termination or expiration will not relieve any Party from obligations which are expressly indicated to survive expiration or termination of this Agreement.

16.4.2 The provisions of Section 2.4.1 (with respect to any Eligible Development Expenses incurred prior to the effective date of termination), Section 3.4.1 (with respect to any Eligible Commercialization Expenses and Eligible Medical Affairs Expenses incurred prior to the effective date of termination), Section 5.3.2, Section 7.1, Section 7.3 (except for the first sentence), Section 8.5, Section 8.7 (only in the event of expiration of this Agreement), Section 8.8, Section 8.9, Section 11.5.2 ([***] with respect to amounts that accrued prior to the effective date of termination), Section 11.5.3 (for final accounting), Section 11.7 (for final accounting), Section 11.10 (with respect to any Other Operating Expenses incurred prior to the effective date of termination), Section 11.11.2, Section 11.11.3, Section 11.12, Section 11.13, Section 11.14, Section 11.15, Section 12.1, Section 12.2.1(c), Section 12.2.2 (solely with respect to Joint Program Patent Rights), Section 14.1 through Section 14.4 (for purposes of Article 15), Section 14.5, Section 16.3, and Section 16.4 and Article 13 (other than Section 13.5), Article 15, and Article 17 (other than Section 17.11) will survive the termination of this Agreement or expiration of this Agreement for any reason, in accordance with their respective terms and conditions, and for the duration stated, and where no duration is stated, will survive indefinitely.

ARTICLE 17
MISCELLANEOUS

17.1 Dispute Resolution.

17.1.1 Resolution by Senior Officers. The Parties will seek to settle amicably any and all disputes, controversies or claims arising out of or in connection with this Agreement. Any dispute between the Parties will be promptly presented to the Senior Officers, or their respective designees, for resolution. Such Senior Officers, or their respective designees, will meet in-person or by teleconference as soon as reasonably possible thereafter, and use their good faith efforts to mutually agree upon the resolution of the dispute, controversy or claim.

17.1.2 Request for Arbitration. If after negotiating in good faith pursuant to Section 17.1.1 the Parties fail after good faith discussions undertaken within reasonable promptness, to reach an amicable agreement within [***], then either Party may upon written notice to the other submit to binding arbitration pursuant to Section 17.1.3; *provided* that, except as set forth in Section 6.6.5(g), any dispute within the JSC's decision-making authority whether or not resolved by the Senior Officers will not be subject to arbitration. No statements made by either Party during such discussions will be used by the other Party or admissible in arbitration or any other subsequent proceeding for resolving the dispute.

17.1.3 Arbitration.

(a) Subject to Section 17.2, any dispute, claim or controversy arising from or related in any way to this Agreement or the interpretation, application, breach, termination or validity thereof, including any claim of inducement of this Agreement by fraud or otherwise, not resolved under the provisions of Section 17.1.2, will be resolved by final and binding arbitration conducted in accordance with the terms of this Section 17.1.3. The arbitration will be held in New York, New York, USA according to Rules of Arbitration of the ICC. The arbitration will be conducted by a panel of three arbitrators with significant experience in the pharmaceutical industry, unless otherwise agreed by the Parties, appointed in accordance with applicable ICC rules. Any arbitration herewith will be conducted in the English language to the maximum extent possible. The arbitrators will render a written decision no later than [***] following the selection of the arbitrators, including a basis for any damages awarded and a statement of how the damages were calculated. Any award will be promptly paid in U.S. dollars free of any tax, deduction or offset. Each Party agrees to abide by the award rendered in any arbitration conducted pursuant to this Section 17.1.3. With respect to money damages, nothing contained herein will be construed to permit the arbitrator or any court or any other forum to award punitive or exemplary damages, except in the case of breach of Article 13. By entering into this agreement to arbitrate, the Parties expressly waive any claim for punitive or exemplary damages, except in the case of breach of Article 13. Each Party will pay its legal fees and costs related to the arbitration (including witness and expert fees). Judgment on the award so rendered will be final and may be entered in any court having jurisdiction thereof.

(b) EACH PARTY HERETO WAIVES ITS RIGHT TO TRIAL OF ANY ISSUE BY JURY. EACH PARTY HERETO WAIVES ANY CLAIM FOR ATTORNEYS' FEES AND COSTS AND PREJUDGMENT INTEREST FROM THE OTHER.

17.1.4 Court Actions. Nothing contained in this Agreement will deny either Party the right to seek injunctive or other equitable relief from a court of competent jurisdiction in the context of a *bona fide* emergency or prospective irreparable harm, and such an action may be filed and maintained notwithstanding any ongoing dispute resolution discussions or arbitration proceeding. In addition, either Party may bring an action in any court of competent jurisdiction to resolve disputes pertaining to the validity, construction, scope, enforceability, infringement or other violations of patents or other proprietary or intellectual property rights, and no such claim will be subject to arbitration pursuant to Section 17.1.2.

17.2 Governing Law; Jurisdiction; Equitable Relief; Losses; Remedies.

17.2.1 This Agreement will be governed by and construed and enforced in accordance with the laws of the State of New York, USA, without reference to any rules of conflicts of laws. For clarification, subject to Section 12.1.2(d), any dispute relating to the scope, validity, enforceability or infringement of any Patent Rights will be governed by and construed and enforced in accordance with the patent laws of the applicable jurisdiction.

17.2.2 Each Party acknowledges and agrees that the restrictions set forth in Section 5.2, Section 8.6, Section 9.2, Section 16.3.3 and Article 13 are reasonable and necessary to protect the legitimate interests of the other Party and that the other Party would not have entered into this Agreement in the absence of such restrictions, and that any breach or threatened breach of any of these provisions will result in irreparable injury to the other Party for which there will be no adequate remedy at law. In the event of a breach or threatened breach of Section 5.2, Section 8.6, Section 9.2, Section 16.3.3 or Article 13, each Party will be authorized and entitled to obtain from any court of competent jurisdiction equitable relief, whether preliminary or permanent, specific performance and an equitable accounting of all earnings, profits and other benefits arising from such breach, which rights will be cumulative and in addition to any other rights or remedies to which such Party may be entitled in law or equity. Each Party agrees to waive any requirement that the other Party (a) post a bond or other security as a condition for obtaining any such relief, and (b) show irreparable harm, balancing of harms, consideration of the public interest or inadequacy of monetary damages as a remedy. Nothing in this Section 17.2.2 is intended, or should be construed, to limit a Party's rights to equitable relief or any other remedy for a breach of any other provision of this Agreement. Except for (i) the offsets and credits explicitly set forth in Section 2.4.1(b)(ii), Section 2.4.1(b)(iii), Section 2.5.4, and Section 11.11.3(c), (ii) any amount awarded to be paid by one Party to the other by the panel of arbitrators in a final and binding arbitration proceeding adjudicated under Section 17.1.3 and (iii) any offset of undisputed but unpaid amounts under this Agreement, neither Party will have the right to set off any amount it is owed or believes it is owed against payments due or payable to the other Party under this Agreement.

17.2.3 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 15.1 or Section 15.2).

17.2.4 Any provisions of this Agreement that describe a payment as non-refundable shall be without prejudice to either Party's right to bring a claim for breach of this Agreement, misrepresentation or any other claim permissible under applicable Laws, including seeking recovery of payments made and damages for loss.

17.3 **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 to which this Agreement or relevant part relates or to any successor corporation resulting from any merger, consolidation, share exchange or other similar transaction; *provided* that, if a Party transfers or assigns this Agreement (or any part hereof) to [***], then such transferring Party (or such Affiliate) ("***Transferring Party***"), will [***]. Any purported assignment or transfer made in contravention of this Section 17.3 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 a [***] the Non-Transferring Party pursuant to the foregoing sentence, beginning with the first annual tax return for the year in which the Transferring Party [***] under this Section 17.3, and each year thereafter (including, for clarity, all years in which the Non-Transferring Party utilizes [***], 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 [***], supporting documentation for such [***].

17.4 **Performance by Affiliates**. Notwithstanding anything to the contrary set forth herein, each Party will have the right to perform any or all of its obligations and exercise any or all of its rights under this Agreement through any of its Affiliates. Each Party hereby guarantees the performance by its Affiliates of such Party's obligations under this Agreement and will cause its Affiliates to comply with the provisions of this Agreement in connection with such performance.

17.5 **Force Majeure**. Neither Party will be held liable or 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 fulfilling or performing any obligation (other than a payment obligation) of this Agreement to the extent such failure or delay is due to force majeure. For purposes of this Agreement, "***Force Majeure***" is defined as any cause beyond the reasonable control of the affected Party and without the fault or negligence of such Party, which may include acts of God; material changes in Law; war; civil commotion; destruction of production facilities or materials by fire, flood, earthquake, explosion or storm; labor disturbances; epidemic; pandemic; quarantine; and failure of public utilities or common carriers. The Parties agree the effects of the COVID-19 pandemic that is ongoing as of the Execution Date (including related government orders) may be invoked as a Force Majeure for the purposes of this Agreement even though the pandemic is ongoing to the extent those effects are not reasonably foreseeable by the Parties as of the Execution Date. Notwithstanding the foregoing, a Party will not be excused from making payments owed hereunder due to any Force Majeure circumstances affecting such Party. In the case of a Force Majeure, the Party affected by such Force Majeure 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 thereupon 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 [***], after which time the Parties will promptly meet to discuss in good faith how to best proceed in a manner that maintains and abides by the Agreement. To the extent possible, the Party affected by such Force Majeure will use reasonable efforts to minimize the duration of any Force Majeure.

17.6 **Notices**. Any notice or request required or permitted to be given under or in connection with this Agreement will be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested) 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 AstraZeneca,

addressed to: AstraZeneca AB
SE-431 83 Mölndal
Sweden
Attention: Legal Department

with a copy to (which shall not constitute notice):

AstraZeneca AB
SE-431 83 Mölndal
Sweden
Attention: Alliance and Integration Management

If to Akcea,

addressed to: Akcea Therapeutics, Inc.
c/o Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Executive Officer
Telephone: [***]

with a copy to (which shall not constitute notice):

Akcea Therapeutics, Inc.
c/o Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
Telephone: [***]
Email: [***]

Ropes & Gray LLP
Prudential Tower
800 Boylston Street
Boston, Massachusetts 02199
Attention: Marc Rubenstein
Telephone: 617-951-7826
Email: marc.rubenstein@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, then 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, then 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, then 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. It is understood and agreed that this Section is not intended to govern the day to day business communications necessary between the parties in performing their duties, in due course, under the terms and conditions of this Agreement.

17.7 **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.

17.8 **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 of such condition or term or of another condition or term except to the extent set forth in writing.

17.9 **Severability**. If any provision hereof should be 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 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.

17.10 **Parent Guaranty**.

17.10.1 Ionis hereby unconditionally, absolutely and irrevocably guarantees, as a primary obligor and not merely as surety, the due and punctual payment and performance of all obligations of Akcea under this Agreement (the "***Akcea Obligations***"). Ionis agrees that the Akcea Obligations may be extended, modified or renewed, in whole or in part, without notice or further assent from it, and that it will remain bound upon its guarantee notwithstanding any extension, modification or renewal of any Akcea Obligation. The obligations of Ionis under this Section 17.10 shall not be affected by (a) the failure of AstraZeneca to assert any claim or demand or to enforce any right or remedy against Akcea under the provisions of this Agreement or otherwise; or (b) any rescission, waiver, amendment or modification of any of the terms or provisions of this Agreement or any other agreement or instrument. Ionis further agrees that its guarantee constitutes a guarantee of payment and performance when due and not of collection and waives any right to require that any resort be had by AstraZeneca to Akcea or to any other guarantee for any security held for payment or performance of the Akcea Obligations. This guarantee shall not be subject to any termination for any reason.

17.10.2 Ionis and Akcea acknowledge and agree that the Ionis/Akcea Agreement shall be subordinate to the provisions of this Agreement, and to the extent any provisions of the Ionis/Akcea Agreement are inconsistent with this Agreement or would impose an additional obligation on, or in any way limit or restrict a right of, AstraZeneca under this Agreement, the terms and conditions of this Agreement shall control, and except for its ownership of all right, title and interest in and to the Licensed Technology, solely for the Territory and solely for the benefit of AstraZeneca, Ionis hereby waives any and all rights it may have under the Ionis/Akcea Agreement that are inconsistent with this Agreement or that would impose an additional obligation on, or in any way limit or restrict a right of, AstraZeneca under this Agreement. Any notice or communication made under this Agreement to or from Akcea shall be deemed to be a notice or communication made to or from Ionis.

17.11 **Change of Control**. If there is a Change of Control of Akcea after the Execution Date, then the following provisions will apply:

17.11.1 Akcea (or its Acquirer) shall provide AstraZeneca with written notice of such Change of Control of Akcea within [***] following the signing date and the closing date of such transaction.

17.11.2 If the Acquirer is Developing or Commercializing a product for an Initial Indication or for any other Indication for which AstraZeneca is Developing or Commercializing the Licensed Product hereunder, then, upon AstraZeneca's request, Akcea and its Acquirer shall establish reasonable procedures, including firewalls between the teams responsible for such product and the teams responsible for the Licensed Product (other than members of senior management of the Acquirer responsible for overall product portfolio management), to prevent the use of any Confidential Information of AstraZeneca or any Patent Rights or Know-How that are subject to a license grant under this Agreement from being used by the Acquirer or its Affiliates in connection with the Development or Commercialization of such product.

17.11.3 If Akcea has not exercised its Opt-Out Right, then AstraZeneca shall [***] and within [***] of the public announcement of the completion of such Change of Control, AstraZeneca shall have the right, by written notice to Akcea, to elect one of the following (and AstraZeneca will be deemed to have elected the effect of clause (a) at the end of such [***] period if it does not otherwise notify Akcea during such [***] period): (a) [***], or (b) [***]; *provided* that, [***]. For clarity, if Akcea [***].

17.12 **Entire Agreement; Amendments**. This Agreement (including the attached Appendices, Exhibits and Schedules) 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 understanding between the Parties regarding the subject matter hereof. In particular, and without limitation, this Agreement supersedes and replaces any and all term sheets relating to the transactions contemplated by this Agreement and exchanged between the Parties prior to the Execution Date. 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 herein. No subsequent alteration, amendment, change or addition to this Agreement will be binding upon the Parties unless reduced to writing and signed by the respective authorized officers of the Parties.

17.13 **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 with respect to the other Party. 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.

17.14 **Headings; Construction; Interpretation**. Headings and any table of contents used herein are for convenience only and will not in any way affect the construction of or be taken into consideration in interpreting this Agreement. The terms and conditions 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 conditions of this Agreement will be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties 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. Any reference in this Agreement to this "*Agreement*" includes the Schedules and Exhibits hereto, the Development Plan and Budget, the U.S. Medical Affairs Plan and Budget, the U.S. Commercialization Plan and Budget and the ROW Commercialization Plan, all of which are incorporated by reference into and constitute a part of this Agreement. Except where explicitly provided, any reference in this Agreement to an Article, Section, subsection, paragraph, clause, Schedule or Appendix will be deemed to be a reference to any Article, Section, subsection, paragraph, clause, Schedule or Appendix, of or to, as the case may be, this Agreement. Except where the context otherwise requires, (a) any definition of or reference to any agreement, instrument or other document refers to such agreement, instrument other document as from time to time amended, supplemented or otherwise modified (subject to any restrictions on such amendments, supplements or modifications set forth herein or therein), (b) any reference to any Law includes all rules and regulations thereunder and any successor Law, in each case as from time to time enacted, repealed or amended, (c) the words "*herein*," "*hereof*" and "*hereunder*," and words of similar import, refer to this Agreement in its entirety and not to any particular provision hereof, (d) the words "*include*," "*includes*," "*including*" will be deemed to be followed by the phrase "*but not limited to*," "*without limitation*" or words of similar import, (e) words in the singular or plural form include the plural and singular form, respectively, (f) references to any gender refer to each gender, (g) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement, (h) the words "*will*" and "*shall*" shall have the same meaning and shall be understood to be imperative or mandatory in nature, (i) the word "*or*" has the inclusive meaning represented by the phrase "*and/or*", (j) a capitalized term not defined herein but reflecting a different part of speech than a capitalized term which is defined herein will be interpreted in a correlative manner, (k) references to a number of days, unless otherwise specified, refers to calendar days, (l) use of the term "*Licensed Compound*" and "*Licensed Product*" shall not be deemed to limit any rights of AstraZeneca with respect to all Licensed Compounds and all Licensed Products and (m) the words "*costs*" and "*expenses*" shall have the same meaning.

17.15 **Further Actions**. Each Party will execute, acknowledge and deliver such further instruments, and do all such other acts, as may be necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

17.16 **Parties in Interest**. All of the terms and provisions of this Agreement will be binding upon, and will inure to the benefit of and be enforceable by the Parties hereto and their respective successors, heirs, administrators and permitted assigns.

17.17 **Counterparts**. This Agreement may be signed in counterparts, each and every one 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 from separate computers or printers. Facsimile signatures and signatures transmitted via PDF will be treated as original signatures.

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

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Parties have caused this Agreement to be executed by their duly authorized representatives as of the Execution Date.

Akcea Therapeutics, Inc.

By: /s/ Brett Monia
Name:Brett Monia
Title:President

AstraZeneca AB (publ)

By: /s/ Elisabeth BjÖrk
Name: Elisabeth Björk
Title: Senior Vice President, Late CVRM

With respect to Article 14 and Section 17.10 only:

Ionis Pharmaceuticals, Inc.

By: /s/ Brett Monia
Name: Brett Monia
Title: Chief Executive Officer

[Signature Page to Collaboration and License Agreement]

Appendix 1

Definitions

For purposes of this Agreement, the following terms will have the meanings set forth below:

1.1 "***Accounting Standards***" means, with respect to a Party, IFRS or GAAP, as applicable, as generally and consistently applied throughout a Party's organization.

1.2 "***Acquirer***" has the meaning set forth in the definition of "*Change of Control*".

1.3 "***Additional Core IP***" means Third Party intellectual property that is necessary to Exploit the Licensed Compound as it is being clinically Developed on the Execution Date and relates generally to the same class of oligonucleotides as eplontersen, including [***] Conjugate Technology.

1.4 "***Additional Development***" has the meaning set forth in Section 2.5.1.

1.5 "***Additional Development Proposal***" has the meaning set forth in Section 2.5.1.

1.6 "***Affiliate***" means any Person that, directly or indirectly through one or more intermediaries, controls, is controlled by or is under common control with a Party to this Agreement at the applicable time. A Person will be deemed to "*control*" another Person if it (a) owns, directly or indirectly, beneficially or legally, 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 Person, or has other comparable ownership interest with respect to any Person other than a corporation; or (b) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of such other Person. For clarity, Ionis is an Affiliate of Akcea.

1.7 "***Agreement***" has the meaning set forth in the Preamble of this Agreement.

1.8 "***Akcea***" has the meaning set forth in the Preamble of this Agreement.

1.9 "***Akcea Core Technology IP***" means the Akcea Core Technology Know-How and the Akcea Core Technology Patent Rights, including, for the avoidance of doubt, any Additional Core IP that Akcea (or its Affiliate) has obtained a license to under Section 11.8.3(a).

1.10 "***Akcea Core Technology Know-How***" means all Know-How, other than Joint Know-How, Controlled by Akcea or its Affiliates on the Execution Date or at any time prior to the end of the Term that (a) is necessary or reasonably useful to Exploit the Licensed Compound or the Licensed Product, and (b) relates generally to oligonucleotides, including Conjugate Technology, in each case *other than* Akcea Product-Specific Know-How or Akcea Manufacturing and Analytical Know-How.

1.11 "***Akcea Core Technology Patent Rights***" means all Patent Rights, other than Joint Patent Rights, Controlled by Akcea or its Affiliates on the Execution Date or at any time prior to the end of the Term that (a) are necessary or reasonably useful to Exploit the Licensed Compound or the Licensed Product, and (b) claim subject matter generally applicable to oligonucleotides, including Conjugate Technology, in each case *other than* Akcea Product-Specific Patent Rights or Akcea Manufacturing Patent Rights. The Akcea Core Technology Patent Rights as of the Execution Date are set forth on Schedule 1.11 attached hereto; provided that, the Patent Rights set forth on Schedule 1.11 shall be considered Akcea Core Technology Patent Rights whether or not such Patent Rights are otherwise described in clause (a) and (b) of this Section 1.11.

1.12 "***Akcea Indemnified Parties***" has the meaning set forth in Section 15.1.

1.13 "***Akcea Internal ASO Safety Database***" has the meaning set forth in Section 4.6.3(a).

1.14 "***Akcea Manufacturing and Analytical Know-How***" means Know-How, other than Joint Know-How, Controlled by Akcea or its Affiliates on the Execution Date or at any time prior to the end of the Term that relates to the synthesis or analysis of an oligonucleotide, including the Licensed Compound or the Licensed Product, regardless of sequence or chemical modification. Akcea Manufacturing and Analytical Know-How includes Akcea Manufacturing Improvements.

1.15 "***Akcea Manufacturing Improvement In-License***" has the meaning set forth in Section 5.3.1(b).

1.16 "***Akcea Manufacturing Improvements***" has the meaning set forth in Section 5.3.1(a).

1.17 "***Akcea Manufacturing IP***" means the Akcea Manufacturing and Analytical Know-How and the Akcea Manufacturing Patent Rights.

1.18 "***Akcea Manufacturing Patent Rights***" means all Patent Rights, other than Joint Patent Rights, Controlled by Akcea or its Affiliates on the Execution Date or at any time prior to the end of the Term that claim the synthesis or analysis of an oligonucleotide, including the Licensed Compound or the Licensed Product, regardless of sequence or chemical modification; *except* Akcea Manufacturing Patent Rights do not include Patent Rights specifically directed to oligonucleotide compounds that specifically modulate expression of TTR via the binding, partially or wholly, of such compound to RNA that encodes TTR (which Patent Rights will be Akcea Product-Specific Patent Rights). Akcea Manufacturing Patent Rights includes Akcea Manufacturing Improvements. The Akcea Manufacturing Patent Rights as of the Execution Date are set forth on Schedule 1.18 attached hereto.

1.19 "***Akcea Obligations***" has the meaning set forth in Section 17.10.1.

1.20 "***Akcea Patent Rights***" means, collectively, the Akcea Core Technology Patent Rights, the Akcea Manufacturing Patent Rights and the Akcea Product-Specific Patent Rights.

1.21 "***Akcea Product-Specific IP***" means the Akcea Product-Specific Know-How and the Akcea Product-Specific Patent Rights.

1.22 "***Akcea Product-Specific Know-How***" means all Know-How, other than Joint Know-How, Controlled by Akcea or its Affiliates on the Execution Date or at any time prior to the end of the Term necessary or reasonably useful to Exploit the Licensed Compound or the Licensed Product, in each case, that specifically relates to (a) the composition of matter of the Licensed Compound or the Licensed Product, or (b) methods of using the Licensed Compound or the Licensed Product as a prophylactic, therapeutic or diagnostic; *provided*, *however*, Know-How Controlled by Akcea or any of its Affiliates to the extent (i) consisting of subject matter applicable to oligonucleotide compounds or products in general, or (ii) relating to an oligonucleotide compound that does not specifically modulate expression of TTR via the binding, partially or wholly, of such compound to RNA that encodes TTR, will not be considered Akcea Product-Specific Know-How. Know-How that would otherwise qualify as Akcea Product-Specific Know-How but for clauses (i) or (ii) will be considered Akcea Core Technology Know-How.

1.23 "***Akcea Product-Specific Patent Rights***" means all Patent Rights, other than Joint Patent Rights, Controlled by Akcea or its Affiliates on the Execution Date or at any time prior to the end of the Term claiming: (a) the specific composition of matter of a Licensed Compound or a Licensed Product, or (b) methods of using a Licensed Compound or a Licensed Product as a prophylactic, therapeutic or diagnostic; *except* for those Patent Rights set forth on Schedule 1.11, which scheduled Patent Rights will be considered Akcea Core Technology Patent Rights. The Akcea Product-Specific Patent Rights as of the Execution Date are set forth on Schedule 1.23 attached hereto; provided that, the Patent Rights set forth on Schedule 1.23 shall be considered Akcea Product-Specific Patent Rights whether or not such Patent Rights are otherwise described in clause (a) or (b) of this Section 1.23.

1.24 "***Akcea Program Technology***" has the meaning set forth in Section 12.1.2(b).

1.25 "***Alliance Manager***" has the meaning set forth in Section 6.8.

1.26 "***Allowable Overruns***" means, on an activity-by-activity basis, any amount that is (a) less than [***]% above the most recent JSC-approved budgeted costs and expenses for the applicable activity for a Calendar Year on a year-to-date basis set forth in any Development Plan and Budget, U.S. Medical Affairs Plan and Budget, or U.S. Commercialization Plan and Budget, as applicable; *provided* that such amount is not attributable to (i) the breach of this Agreement by the incurring Party or (ii) the gross negligence or willful misconduct of the incurring Party or any of its Affiliates or (b) otherwise approved by the JSC.

1.27 "***Antitrust Authorities***" means the United States Federal Trade Commission and the Antitrust Division of the United States Department of Justice.

1.28 "***Antitrust Filings***" has the meaning set forth in Section 10.2.1.

1.29 "***API***" means the bulk active pharmaceutical ingredient manufactured in accordance with cGMP (unless expressly stated otherwise) for a Licensed Product. The quantity of API will be the as-is gross mass of the API after lyophilization (*i.e.*, including such amounts of water, impurities, salt, heavy, metals, etc. within the limits set forth in the API specifications) and before release, retention, stability or characterization samples are removed (if needed).

1.30 "***Arbitration Proposal***" has the meaning set forth in Schedule 16.3.3(a)(ii).

1.31 "***ASO***" means a single-stranded or double-stranded oligonucleotide compound, or analog, variant, mimic, or mimetic thereof, having a sequence that is between six and one hundred nucleotides long and is designed to hybridize to a nucleic acid transcript via the binding, partially or wholly, of such compound to such nucleic acid transcript.

1.32 "***AstraZeneca***" has the meaning set forth in the Preamble of this Agreement.

1.33 "***AstraZeneca Indemnified Parties***" has the meaning set forth in Section 15.2.

1.34 "***AstraZeneca IP***" means, collectively, (a) the AstraZeneca Know-How, (b) the AstraZeneca Patent Rights and (c) AstraZeneca's interest in the Joint Program Technology.

1.35 "***AstraZeneca Know-How***" means all Know-How, other than Joint Know-How, Controlled by AstraZeneca on the Execution Date or at any time prior to the end of the Term that is necessary to perform Akcea's U.S. Development Activities, Global Development Activities or Co-Commercialization and Medical Affairs Activities, in each case, as set forth in the Development Plan and Budget, U.S. Commercialization Plan and Budget or U.S. Medical Affairs Plan and Budget, as applicable.

1.36 "***AstraZeneca Manufacturing Improvement In-License***" has the meaning set forth in Section 5.3.2(b).

1.37 "***AstraZeneca Manufacturing Improvements***" has the meaning set forth in Section 5.3.2(a).

1.38 "***AstraZeneca Patent Rights***" means all Patent Rights, other than Joint Patent Rights, Controlled by AstraZeneca on the Execution Date or at any time prior to the end of the Term that is necessary to perform Akcea's U.S. Development Activities, Global Development Activities or Co-Commercialization and Medical Affairs Activities, in each case, as set forth in the Development Plan and Budget, U.S. Commercialization Plan and Budget or U.S. Medical Affairs Plan and Budget, as applicable.

1.39 "***AstraZeneca Program Technology***" has the meaning set forth in Section 12.1.2(a).

1.40 "***AstraZeneca Prosecuted Patents***" has the meaning set forth in Section 12.2.2(b).

1.41 "***AstraZeneca Reversion IP***" means the AstraZeneca Reversion Know-How and AstraZeneca Reversion Patent Rights.

1.42 "***AstraZeneca Reversion Know-How***" means all Know-How, other than Joint Know-How, Controlled by AstraZeneca as of the effective date of termination that is necessary or that is actually being used as of the effective date of termination to Exploit the Licensed Compound or the Licensed Product in the applicable Terminated Territory as such Licensed Product is being clinically Developed or Commercialized by AstraZeneca or its Affiliates in the applicable Terminated Territory as of the effective date of termination, but excluding any Know-How that is (a) related to [***], or (b) (i) related to [***], or (ii) [***] as of the effective date of termination to Exploit the Licensed Product as it is being Commercialized by AstraZeneca or its Affiliates in the applicable Terminated Territory as of the effective date of termination.

1.43 "***AstraZeneca Reversion Patent Rights***" means all Patent Rights, other than Joint Patent Rights, Controlled by AstraZeneca as of the effective date of termination that are necessary or that are actually being used as of the effective date of termination to Exploit the Licensed Compound or the Licensed Product in the applicable Terminated Territory as such Licensed Product is being clinically Developed or Commercialized by AstraZeneca or its Affiliates in the applicable Terminated Territory as of the effective date of termination, but excluding any Patent Right that (a) [***], or (b) (i) claims [***], or (ii) [***] as of the effective date of termination to Exploit the Licensed Product as it is being Commercialized by AstraZeneca or its Affiliates in the applicable Terminated Territory as of the effective date of termination.

1.44 "***AstraZeneca Third Party Product-Specific License***" has the meaning set forth in Section 11.8.2.

1.45 "***Auditor***" has the meaning set forth in Section 11.11.3(d).

1.46 "***Authorized CMO***" has the meaning set forth in Section 8.3.2.

1.47 "***Breaching Party***" has the meaning set forth in Section 16.2.1(a).

1.48 "***Business Day***" means any day, other than Saturday, Sunday, or any statutory holiday or bank holiday in the United States or London, England.

1.49 "***Calendar Quarter***" means a period of three consecutive months corresponding to the Calendar Year commencing on January 1, April 1, July 1 and October 1, except that the first Calendar Quarter of the Term shall commence on the Closing Date and end on the day immediately prior to the first to occur of January 1, April 1, July 1 or October 1 after the Closing Date and the last Calendar Quarter shall end on the last day of the Term.

1.50 "***Calendar Year***" means a period of 12 consecutive months corresponding to the Calendar Year commencing on the first day of January, except that the first Calendar Year of the Term shall commence on the Closing Date and end on December 31 of the year in which the Closing Date occurs and the last Calendar Year of the Term shall commence on January 1 of the year in which the Term ends and end on the last day of the Term.

1.51 "***Change of Control***" means, with respect to a Party (a) the acquisition of beneficial ownership, directly or indirectly, by any Third Party (or group of Third Parties) of securities or other voting interest of such Party (or any controlling Affiliate of such Party) representing 50% or more of the combined voting power of such Party's (or any controlling Affiliate of such Party's) then outstanding securities or other voting interests, (b) any merger, reorganization, consolidation or business combination involving such Party (or any controlling Affiliate of such Party) with a Third Party that results in the holders of beneficial ownership (other than by virtue of obtaining irrevocable proxies) of the voting securities or other voting interests of such Party (or any controlling Affiliate of such Party) immediately prior to such merger, reorganization, consolidation or business combination ceasing to hold beneficial ownership of more than 50% of the combined voting power of the surviving entity (or any controlling Affiliate of such Party) immediately after such merger, reorganization, consolidation or business combination, or (c) any sale, lease, exchange, contribution or other transfer to a Third Party (in one transaction or a series of related transactions) of all or substantially all of the assets of such Party (or any controlling Affiliate of such Party) to which this Agreement relates. The acquiring or combining Third Party in any of clause (a), (b) or (c), is referred to herein as the "***Acquirer***".

1.52 "***Clinical Trial***" means any human clinical trial for a product, including (a) a Phase 1 Clinical Trial, Phase 2 Clinical Trial, or Phase 3 Clinical Trial, and (b) any human clinical trial in any country after Regulatory Approval, including (i) clinical trials conducted voluntarily after Regulatory Approval for enhancing marketing or scientific knowledge of an approved Indication, (ii) trials conducted after Regulatory Approval due to a request or requirement of a Regulatory Authority or as a condition of a previously granted Regulatory Approval, and (iii) any REMS/RMP related study after Regulatory Approval.

1.53 "***Closing***" has the meaning set forth in Section 10.1.

1.54 "***Closing Date***" has the meaning set forth in Section 10.1.

1.55 "***CM***" means transthyretin-mediated amyloid cardiomyopathy. For the avoidance of doubt, CM includes cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis.

1.56 "***CMO***" means a Third Party primarily engaged in the business of providing contract manufacturing or manufacturing services.

1.57 "***Co-Commercialization and Medical Affairs Activities***" has the meaning set forth in Section 3.2.2.

1.58 "***COGS***" means, with respect to a Licensed Product, the standard cost of such Licensed Product calculated as the fully absorbed cost of the Manufacturing Party incurred in the Manufacture of that Licensed Product ready for delivery from such Party, as calculated in a manner consistent with the methodology and internal accounting policies employed by such Party for other products, excluding, unless and until the Opt-Out Date (if any), any costs or expenses included as Eligible Expenses other than COGS.

1.59 "[***]" has the meaning set forth in Section 11.5.2.

1.60 "[***]" means [***].

1.61 "***Commercialization***" and "***Commercialize***" means any and all activities undertaken relating to the marketing, obtaining Pricing and Reimbursement Approvals, post-approval commitments, other phase IV studies, promotion (including advertising or detailing), or any other offering for sale or any sale of a product, including any distribution, importation, exportation or transport of a product for sales purposes. "***Commercialization***" will not include Development or Manufacturing.

1.62 "***Commercialization and Medical Affairs Cost Share Notice***" has the meaning set forth in Section 3.4.1(b)(i).

1.63 "***Commercially Reasonable Efforts***" means:

(a) with respect to AstraZeneca, efforts to achieve an objective under this Agreement, including Development and Commercialization objectives, that are not less than the [***], to other compounds and products of similar commercial potential and in a similar commercial space at a similar stage in its lifecycle, taking into consideration relative safety and efficacy, product profile, the competitiveness of the marketplace, market potential, the relative profitability of the product (including pricing and reimbursement status) and other relevant factors, including technical, legal, scientific and medical factors, and

(b) with respect to Akcea, efforts to achieve an objective under this Agreement, including Development and Commercialization objectives, that are not less than the [***] to other compounds and products of similar commercial potential and in a similar commercial space at a similar stage in its lifecycle, taking into consideration relative safety and efficacy, product profile, the competitiveness of the marketplace, market potential, the relative profitability of the product (including pricing and reimbursement status) and other relevant factors, including technical, legal, scientific and medical factors.

With respect to an activity that is subcontracted by either AstraZeneca or Akcea, "Commercially Reasonable Efforts" means the exercise of such care and the dedication of such efforts with respect to: the selection of a subcontractor, the entry into the subcontract with such subcontractor, and the management of such subcontract (including, if applicable, the enforcement thereof), as are commercially reasonable. "Commercially Reasonable Efforts" will be determined on a country-by-country basis in the relevant countries, and activities that are or are not conducted in one country or factors that stem from one country, in each case, that have an effect on achieving the relevant objective in another country will be considered in determining whether Commercially Reasonable Efforts have been applied in such other country.

1.64 "***Competitive Infringement***" has the meaning set forth in Section 12.4.

1.65 "***Competitive Oligo***" means a pharmaceutical or biological product that comprises an ASO and is designed to bind to the RNA of TTR and reduce or block the production of the TTR protein.

1.66 "***Complete,***" "***Completed***," or "***Completion***" means, with respect to a Clinical Trial, the point in time at which database lock for such trial has occurred and the primary and secondary endpoints and key safety data (including tables, listings and figures generated based on that database lock) for such trial are available.

1.67 "***Compulsory Sublicensee***" has the meaning set forth in Section 11.6.2(c).

1.68 "***Confidential Information***" has the meaning set forth in Section 13.1.

1.69 "***Conjugate Technology***" means chemistry that is attached to an ASO and designed to enhance targeting or uptake 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 or uptake of antisense drugs to the liver.

1.70 "***Continuing Party***" has the meaning set forth in Section 12.2.1(c).

1.71 "***Control***" or "***Controlled***" means, with respect to a Party and any intellectual property right or other intangible property, the possession by such Party of the ability to grant a license or sublicense hereunder without violating the terms of any agreement with any Third Party. Notwithstanding anything in this Agreement to the contrary, a Party will be deemed to not Control any intellectual property that is owned or controlled by an Acquirer or such Acquirer's Affiliates (other than the Change of Control Party and any Affiliate of such Party prior to the Change of Control and any successor entity to the Change of Control Party or any such Affiliates thereof (each, a "***Party Affiliate***")), (a) prior to the closing of such Change of Control, except to the extent that any such intellectual property (i) was developed prior to such Change of Control through the use of any intellectual property of a Party Affiliate or any Confidential Information of the other Party or (ii) is used by or on behalf of such Party or any of its Affiliates in performing its obligations under this Agreement, or (b) after such Change of Control, to the extent that such intellectual property (i) is developed or conceived by such Third Party or its Affiliates (other than a Party Affiliate) after such Change of Control without using or incorporating any intellectual property of a Party Affiliate or any Confidential Information of the other Party, (ii) is not used by or on behalf of such Party or any of its Affiliates in performing its obligations under this Agreement, and (iii) is not incorporated into any Licensed Compound or Licensed Product.

1.72 "***Cost Sharing Cap***" has the meaning set forth in Section 3.2.3(b).

1.73 "***Cover***" or "***Covered***" or "***Covering***" means, with respect to a Patent Right and a Licensed Product, that, but for ownership of or rights granted to a Person under such Patent Right the act of making, using, or selling of such Licensed Product by such Person would infringe a Valid Claim included in such Patent Right, or in the case of a Patent Right that is a patent application, would infringe a Valid Claim in such patent application if it were to issue as a patent.

1.74 "***CSO***" means a Third Party primarily engaged in contract sales services with respect to pharmaceutical products, including marketing, sales promotion activities, and related training.

1.75 "***Cure Period***" has the meaning set forth in Section 16.2.1(a).

1.76 "***Current Year Percentage Cap***" means [***]%.

1.77 "***Declining Party***" has the meaning set forth in Section 12.2.1(c).

1.78 "***Default Notice***" has the meaning set forth in Section 16.2.1(a).

1.79 "***Develop***" or "***Development***" means research, including pre-clinical and clinical research and development activities, including drug metabolism and pharmacokinetics, translational research, toxicology, pharmacology toxicology studies, statistical analysis and report writing, formulation development and optimization, Clinical Trials, regulatory affairs (including preparation for a Regulatory Approval Application submission and other submission-related activities), product approval and registration activities, and all activities necessary for obtaining and maintaining Regulatory Approvals, and fulfilling all regulatory obligations, excluding post-approval commitments and other phase IV studies. "***Development***" will not include Commercialization or Manufacturing.

1.80 "***Development Cost Share Notice***" has the meaning set forth in Section 2.4.1(b)(i).

1.81 "***Development Plan and Budget***" has the meaning set forth in Section 2.2.1.

1.82 "***Device***" has the meaning set forth in the definition of "*Net Sales*".

1.83 "***Disclosing Party***" has the meaning set forth in Section 13.1.

1.84 "***Dollars***" or "***$***" means the legal tender of the United States.

1.85 "***Eligible Commercialization Expenses***" means all FTE Costs and Out-of-Pocket Costs incurred by or on behalf of a Party or its Affiliates after the Closing Date that are, unless specifically stated otherwise, reasonably allocable to Commercialization activities for the Licensed Product in the U.S. (including Manufacturing in support thereof) after the Closing Date and prior to the Opt-Out Date, in each case, to the extent such activities are in furtherance of the objectives set forth in the U.S. Commercialization Plan and Budget and, except with respect to clause (f), such costs are consistent with the U.S. Commercialization Plan and Budget, *plus* Allowable Overruns, but expressly excluding Non-Reimbursable Expenses. Subject to the foregoing, Eligible Commercialization Expenses includes the following:

(a) [***];

(b) [***];

(c) [***];

(d) [***];

(e) [***];

(f) [***]; and

(g) any other categories of expenses expressly identified in the U.S. Commercialization Plan and Budget (*provided* that, in the event of a conflict regarding a category of expenses to be included in the U.S. Commercialization Plan and Budget and any provision of this Agreement that specifies that such category of expenses will be treated in a different manner (including, for example, by treating such category of expenses as included in Eligible Development Expenses), then the provisions of this Agreement shall control unless the U.S. Commercialization Plan and Budget expressly states that it is intended to override such provision of this Agreement);

If any FTE Cost, Out-of-Pocket Cost, or other cost or expense is included in more than one category of Eligible Commercialization Expenses set forth above, then such cost or expense will only be counted once (*i.e.*, as an Eligible Commercialization Expense with respect to only one such category). No FTE Cost, Out-of-Pocket Cost, or other cost or expense included as an Eligible Commercialization Expense will also be included as an Eligible Development Expense, an Eligible Medical Affairs Expense, or an Other Operating Expense.

1.86 "***Eligible Development Expenses***" means all FTE Costs and Out-of-Pocket Costs incurred by or on behalf of a Party or its Affiliates after the Closing Date (except with respect to clause (c) which may include FTE Costs and Out-of-Pocket Costs incurred by or on behalf of a Party or its Affiliates before the Closing Date) that are, unless specifically stated otherwise, reasonably allocable to Development of the Licensed Product (including Manufacturing in support thereof) after the Closing Date and, except with respect to Section 3.6.2(a)(i), prior to the Opt-Out Date, in each case, to the extent such activities are in furtherance of the objectives set forth in the Development Plan and Budget and such costs are consistent with the Development Plan and Budget, *plus* Allowable Overruns, but expressly excluding Non-Reimbursable Expenses. Subject to the foregoing, Eligible Development Expenses includes:

(a) [***];

(b) [***];

(c) [***];

(d) [***];

(e) [***];

(f) [***]; and

(g) any other categories of expenses expressly identified in the Development Plan and Budget *(provided* that, in the event of a conflict regarding a category of expenses to be included in the Development Plan and Budget and any provision of this Agreement that specifies that such category of expenses will be treated in a different manner (including, for example, by treating such category of expenses as included in Eligible Commercialization Expenses), then the provisions of this Agreement shall control unless the Development Plan and Budget expressly states that it is intended to override such provision of this Agreement);

If any FTE Cost, Out-of-Pocket Cost, or other cost or expense is included in more than one category of Eligible Development Expenses above, then such cost or expense will only be counted once. No expense included as an Eligible Development Expense will also be included as an Eligible Commercialization Expense, an Eligible Medical Affairs Expense, or an Other Operating Expense. Eligible Development Expenses will not include any FTE Cost, Out-of-Pocket Cost, or other cost or expense associated with the Manufacture of the Licensed Product for commercial sale.

1.87 "***Eligible Expenses***" means Eligible Development Expenses, Eligible Commercialization Expenses, Eligible Medical Affairs Expenses and Other Operating Expenses.

1.88 "***Eligible Medical Affairs Expenses***" means all FTE Costs and Out-of-Pocket Costs incurred by or on behalf of a Party or its Affiliates after the Closing Date that are, unless specifically stated otherwise, reasonably allocable to Medical Affairs activities for the Licensed Product in the U.S. after the Closing Date and prior to the Opt-Out Date, in each case, to the extent such activities are in furtherance of the objectives set forth in the U.S. Medical Affairs Plan and Budget and such costs are consistent with the U.S. Medical Affairs Plan and Budget, *plus* Allowable Overruns, but expressly excluding Non-Reimbursable Expenses. Subject to the foregoing, Eligible Medical Affairs Expenses includes:

(a) [***];

(b) [***];

(c) [***];

(d) [***];

(e) [***]; and

(f) any other categories of expenses expressly identified in the U.S. Medical Affairs Plan and Budget (*provided* that, in the event of a conflict regarding a category of expenses to be included in the U.S. Medical Affairs Plan and Budget and any provision of this Agreement that specifies that such category of expenses will be treated in a different manner (including, for example, by treating such category of expenses as included in Eligible Commercialization Expenses), then the provisions of this Agreement shall control unless the U.S. Medical Affairs Plan and Budget expressly states that it is intended to override such provision of this Agreement);

If any FTE Cost, Out-of-Pocket Cost, or other cost or expense is included in more than one category of Eligible Medical Affairs Expenses set forth above, then such cost or expense will only be counted once (*i.e.*, as an Eligible Medical Affairs Expenses with respect to only one such category). No expense included as an Eligible Medical Affairs Expense will also be included as an Eligible Development Expense, Eligible Commercialization Expense, or an Other Operating Expense.

1.89 "***EMA***" means the European Medicines Agency, and any successor entity thereto.

1.90 "***EU***" means the member countries of the European Union as of the Execution Date. Notwithstanding the foregoing, the EU will be deemed to include the United Kingdom.

1.91 "***Exchange Rate***" has the meaning set forth in Section 11.14.

1.92 "***Exclusivity Period***" has the meaning set forth in Section 9.2.

1.93 "***Execution Date***" has the meaning set forth in the Preamble of this Agreement.

1.94 "***Existing In-License Agreements***" means those Akcea in-license agreements set forth on Schedule 1.94 attached hereto.

1.95 "***Exploit***" or "***Exploitation***" means to make, have made, export, have exported, import, have imported, use, have used, sell, have sold, offer for sale, Develop, have Developed, Manufacture, have Manufactured, Commercialize, have Commercialized and otherwise exploit and have exploited.

1.96 "***FDA***" means the U.S. Food and Drug Administration, and any successor entity thereto.

1.97 "***Field***" means all human and non-human diagnostic, prophylactic and therapeutic uses.

1.98 "***First Commercial Sale***" means the first sale of the Licensed Product by AstraZeneca, its Affiliate or Sublicensee to a Third Party in a particular country in the Territory after Regulatory Approval (other than Pricing and Reimbursement Approvals) of such Licensed Product has been obtained in such country.

1.99 "***First Opt-Out Period***" has the meaning set forth in Section 3.6.1.

1.100 "***Force Majeure***" has the meaning set forth in Section 17.5.

1.101 "***FTE***" means the efforts of one or more employees of a Party (or its Affiliate) equivalent to the efforts of one full-time employee for one year, or in the case of less than a full-time dedicated person, a full-time equivalent person-year, in each case, based upon a total of 1,710 hours per year of work; *provided* that any such employee who devotes fewer than 1,710 hours per year under this Agreement shall be treated as an FTE on a *pro rata* basis based on the number of hours worked under this Agreement (based on such Party's internal tracking processes) divided by 1,710.

1.102 "***FTE Costs***" means the product of the number of FTEs and the FTE Rate.

1.103 "***FTE Rate***" means [***] per FTE for the period commencing on the Closing Date and ending December 31, 2022. On January 1, 2023 and on January 1st of each subsequent Calendar Year, the foregoing rate will be adjusted for the Calendar Year then commencing by the [***]; *provided*, *however*, that in no event will such adjustment result in an FTE Rate less than [***]. As used in this Section 1.103, [***].

1.104 "***Future In-License Agreement***" means any agreement between Akcea or its Affiliate, on the one hand, and a Third Party, on the other hand, that is entered into after the Execution Date and pursuant to which Akcea acquires Control of any Licensed Technology.

1.105 "***GAAP***" means United States generally accepted accounting principles consistently applied.

1.106 "***Generic Intrusion***" means, with respect to a Licensed Product in a particular country in the Territory (the "***Reference Product***"), when the Generic Products have, in the aggregate, achieved more than [***]% of the market share in such country by unit volume (based on data provided by IQVIA or another reliable Third Party data source mutually agreed by the Parties) of combined unit sales of the Reference Product and all Generic Products.

1.107 "***Generic Product***" means, with respect to the Reference Product in a particular country in the Territory, any pharmaceutical product sold by a Third Party that is not authorized by AstraZeneca (other than through a Settlement Sublicense) that:

(a) (i) contains the same active pharmaceutical ingredient as the Reference Product, and (ii) is approved in reliance, in whole or in part, on a prior Regulatory Approval of the Reference Product (or data submitted in support of such Regulatory Approval); or

(b) (i) is approved in reliance, in whole or in part, on a prior Regulatory Approval of the Reference Product (or data submitted in support of such Regulatory Approval) and (ii) is determined by the applicable Regulatory Authority to be substitutable for the Reference Product.

1.108 "***Global Development Activities***" has the meaning set forth in Section 2.4.1.

1.109 "***Good Clinical Practices***" or "***cGCP***" means the then-current standards, practices, procedures and regulatory requirements promulgated or endorsed by the FDA and its applicable foreign counterparts, including the guidelines adopted by the ICH, titled "*Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance*".

1.110 "***Good Laboratory Practices***" or "***cGLP***" means the then-current good laboratory practice standards promulgated or endorsed by the FDA, as defined in U.S. 21 C.F.R. Part 58, and such comparable regulatory standards in those applicable jurisdictions outside of the United States.

1.111 "***Good Manufacturing Practices***" or "***cGMP***" means the then-current good manufacturing practices and standards promulgated or endorsed by the FDA, as provided for in the Current Good Manufacturing Practice Regulations of the U.S. Code of Federal Regulations Title 21 (21 C.F.R. §§210 and 211), and such comparable regulatory standards in those applicable jurisdictions outside of the United States, including the guidelines adopted by the ICH, titled, "*Good Manufacturing Practice Guide for Active Ingredients, Q7*".

1.112 "***Government Official***" means: (a) any elected or appointed government official (*e.g.*, a member of a ministry of health), (b) any employee or person acting for or on behalf of a government official, agency, or enterprise performing a governmental function, (c) any political party officer, employee, or person acting for or on behalf of a political party or candidate for public office, (d) an employee or person acting for or on behalf of a public international organization, or (e) any person otherwise categorized as a government official under local Law. As used herein, "*government*" is meant to include all levels and subdivisions of non-U.S. governments (*i.e.*, local, regional, or national and administrative, legislative, or executive).

1.113 "***Governmental Authority***" means any court, agency, department, authority or other instrumentality of any national, state, county, city or other political subdivision.

1.114 "***HSR Act***" means the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the rules and regulations promulgated thereunder.

1.115 "***HSR Clearance***" has the meaning set forth in Section 10.1.

1.116 "***ICH***" means the International Council for Harmonization.

1.117 "***IFRS***" means international financial reporting standards, consistently applied.

1.118 "***In-License Agreement***" means (a) any Existing In-License Agreement, and (b) any Future In-License Agreement, in each case of (a) and (b), as amended from time to time.

1.119 "***Inbound Licensor***" means any Third Party licensor under any of the In-License Agreements.

1.120 "***Included FTE Costs and Expenses***" means the sum of (a) [***], (b) [***] and (c) [***], in each case ((a), (b) and (c)), (i) [***], and (ii) except as may be specifically agreed otherwise as an item included in the budget in the then-current Development Plan and Budget, U.S. Commercialization Plan and Budget or U.S. Medical Affairs Plan and Budget, as applicable.

1.121 "***IND***" means an investigational new drug application submitted to the FDA pursuant to Part 312 of Title 21 of the U.S. Code of Federal Regulations, including any amendments thereto. References herein to IND will include, to the extent applicable, any comparable filing(s) outside the U.S. for the investigation of any product in any other country or group of countries.

1.122 "***Indemnification Claim Notice***" has the meaning set forth in Section 15.4.1.

1.123 "***Indemnified Party***" has the meaning set forth in Section 15.4.1.

1.124 "***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*") requiring a separate Phase 3 Clinical Trial to obtain Regulatory Approval to market and sell the Licensed Product for such disease, and will include sub-types of the same disease and pediatric populations of the same disease (*i.e.*, such sub-types and pediatric populations shall be part of the same Indication and shall not be treated as a separate Indication).

1.125 "***Indirect Taxes***" means value added taxes, sales taxes, consumption taxes and other similar taxes required by applicable Law to be disclosed on the invoice.

1.126 "***Initial Indication***" means, with respect to the Licensed Product, each of (a) PN and (b) CM.

1.127 "***Inotersen***" means the compound having the following sequence and chemistry: 5′-^{Me}U^{Me}C^{Me}U^{Me}UGGTTA^{Me}CATGAAA^{Me}U^{Me}C^{Me}C^{Me}C- 3.′ The underlined residues are 2'-O-(2-methoxyethyl) nucleosides (2'-MOE nucleosides). The residues are arranged so that there are five 2'-MOE nucleosides at the 5′ and 3′-ends of the molecule flanking a gap of ten 2′-deoxynucleosides. The cytosine and uracil bases are methylated at the 5-position. ^{Me}U and T have the same nucleobase structure and the choice for the symbol depends on whether the sugar is 2′-deoxy-D-ribose or D-ribose. Each of the 19 internucleoside linkages is a phosphorothioate linkage. Inotersen does not include any product containing Conjugate Technology.

1.128 "***Inotersen Product***" means any pharmaceutical preparation that (a) contains Inotersen as an active pharmaceutical ingredient and (b) does not contain any other ASO that is designed to bind to the RNA of TTR and reduce or block the production of the TTR protein.

1.129 "***Interim U.S. Commercialization Plan and Budget***" has the meaning set forth in Section 3.2.1(a).

1.130 "***Interim U.S. Medical Affairs Plan and Budget***" has the meaning set forth in Section 3.2.2(a).

1.131 "***Ionis***" has the meaning set forth in the Preamble of this Agreement.

1.132 "***Ionis/Akcea Agreement***" has the meaning set forth in the Recitals of this Agreement.

1.133 "***Joint Commercialization and Medical Committee***" or "***JCMC***" has the meaning set forth in Section 6.4.1.

1.134 "***Joint Development Committee***" or "***JDC***" has the meaning set forth in Section 6.3.1.

1.135 "***Joint Know-How***" has the meaning set forth in Section 12.1.2(c).

1.136 "***Joint Patent Rights***" has the meaning set forth in Section 12.1.2(c).

1.137 "***Joint Program Technology***" has the meaning set forth in Section 12.1.2(c).

1.138 "***Joint Steering Committee***" or "***JSC***" has the meaning set forth in Section 6.1.1.

1.139 "***Know-How***" means all information, know-how and data, including trade secrets, inventions (whether patentable or not), discoveries, developments, methods, specifications, processes, expertise, techniques, technologies, other non-clinical, pre-clinical and clinical data, documentation and results (including pharmacological, toxicological, biological, chemical, physical, safety and manufacturing data and results), analytical and quality control data and results, Regulatory Filings and other technical information, in each case, whether or not patentable or copyrightable and that are not Covered by an issued Patent Right or otherwise publicly available. "***Know-How***" excludes any Patent Rights.

1.140 "***Knowledge***" means the good faith, actual understanding of the facts and information by a Party's or any of its Affiliate's executive officers and their attorneys employed in their Legal Department and Patent Department as of the Execution Date; *provided* that, with respect to information regarding the status of Patent Rights or other intellectual property rights, "Knowledge" means the good faith, actual understanding of the facts and information by a Party's or any of its Affiliate's executive officers and their attorneys employed in their Legal Department and Patent Department as of the Execution Date after performing a diligent investigation with respect to such facts and information as is customary in the conduct of its business with respect to such Patent Rights or other intellectual property rights (and not, for clarity, a diligent investigation solely in connection with this Agreement).

1.141 "***Last Approved Budget***" means, with respect to a Reference Calendar Year, the sum of (a) [***] and (b) [***]; *provided, however,* that if [***], then the budget used for purposes of clause (a) or clause (b), as applicable, shall be [***].

1.142 "***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.

1.143 "***Lead Development Party***" has the meaning set forth in Section 2.2.2.

1.144 "***Licensed Compound***" mean (a) the ASO compound known as eplontersen (ION-682884), and (b) any other ASO (other than Inotersen) that is (i) discovered, owned or in-licensed by Akcea or any of its Affiliates as of the Execution Date and (ii) designed to bind to the RNA of TTR and reduce or block the production of transthyretin, or TTR protein, including, in each case ((a) and (b)), any salt, hydrate, solvate or pro-drug thereof.

1.145 "***Licensed Product***" means any pharmaceutical product, in any form, presentation, delivery system, dosage or formulation, containing a Licensed Compound, either alone or in combination with one or more other active pharmaceutical ingredients.

1.146 "***Licensed Technology***" means, collectively, (a) the Akcea Core Technology IP, (b) the Akcea Manufacturing IP, (c) the Akcea Product-Specific IP, (d) Akcea's interest in the Joint Program Technology and (e) any other intellectual property Controlled by Akcea or its Affiliates on the Execution Date or any time prior to the end of the Term that Covers, or the use of which is necessary or reasonably useful to Exploit, the Licensed Compound or the Licensed Product.

1.147 "***Losses***" has the meaning set forth in Section 15.1.

1.148 "***MAA***" means, with respect to the Licensed Product, a marketing authorization application filed with the EMA after Completion of Clinical Trials to obtain Regulatory Approval for the Licensed 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.

1.149 "***Major Market***" means any of the following countries: the United States, France, Germany, Italy, Spain, and the United Kingdom.

1.150 "***Manufacture***" or "***Manufacturing***" means all activities related to the manufacturing of an active pharmaceutical ingredient or product or any component thereof, including test method development and stability testing, formulation, process development, manufacturing scale-up, manufacturing for use in non-clinical and clinical studies, manufacturing for commercial sale, packaging, release of product, quality assurance/quality control development, quality control testing (including in-process, in-process release and stability testing) and release of product or any component or ingredient thereof, and regulatory activities related to all of the foregoing. "***Manufacturing***" will not include Development or Commercialization.

1.151 "***Manufacturing Transition Plan***" has the meaning set forth in Section 5.2.1.

1.152 "***Medical Affairs***" means activities conducted by a Party's medical affairs departments (or, if a Party does not have a medical affairs department, the equivalent function thereof), including real world evidence, communications with key opinion leaders, continuing medical education, symposia, advisory boards (to the extent related to medical affairs or clinical guidance), activities performed in connection with patient registries, and other similar medical programs and communications.

1.153 "***MHRA***" means the Medicines and Healthcare products Regulatory Agency, and any successor entity thereto.

1.154 "***NDA***" means a New Drug Application (as more fully described in 21 C.F.R. 314.50 et seq. or its successor regulation) and all amendments and supplements thereto filed with the FDA.

1.155 "***Negotiation Period***" has the meaning set forth in Section 9.1.

1.156 "***Net Sales***" means, with respect to a Licensed Product, the gross invoiced amount on sales of such Licensed Product by or on behalf of AstraZeneca, its Affiliates, and its and their Sublicensees to Third Parties (which Third Parties will include distributors) after deduction of the following amounts, to the extent taken:

(a) normal and customary trade, quantity or prompt settlement discounts (including initial launch stocking discounts, chargebacks and allowances) actually allowed, *provided* that such discounts are not applied disproportionately to such Licensed Product when compared to the other products of AstraZeneca, its Affiliates or its or their Sublicensees, as applicable;

(b) amounts repaid or credited by reason of rejection, returns or recalls of goods, rebates or bona fide price reductions determined by AstraZeneca, its Affiliates or its or their Sublicensees in good faith;

(c) rebates and similar payments made with respect to sales paid for by any Governmental Authority such as, by way of illustration and not in limitation of the Parties' rights hereunder, Federal or state Medicaid, Medicare or similar state program in the United States or equivalent governmental program in any other country;

(d) any invoiced amounts that are not collected by AstraZeneca, its Affiliates or its or their Sublicensees, including bad debts;

(e) excise taxes, value added taxes, sales taxes, consumption taxes and other similar taxes (excluding any income, franchise or withholding taxes), customs duties, customs levies and import fees imposed on the sale, importation, use or distribution of the Licensed Product, including fees paid pursuant to Section 9008 of the Patient Protection and Affordable Care Act that AstraZeneca, its Affiliates or its or their Sublicensees, as applicable, allocable to sales of the Licensed Product in accordance with AstraZeneca's, its Affiliates' or its or their Sublicensees' standard policies and procedures consistently applied across its products, as applicable;

(f) the portion of administrative fees paid during the relevant time period to group purchasing organizations or pharmaceutical benefit managers relating to the Licensed Product;

(g) service fees payable under any wholesaler agreement, distribution services agreement, inventory management agreement or other similar agreement;

(h) any other similar and customary deductions (including co-pay cards) that are consistent with the United States generally accepted accounting principles or, in the case of non-United States sales, other applicable accounting standards;

(i) an allowance for transportation costs, distribution expenses, special packaging and related insurance charges equal to three percent (3%) of the amount arrived at after application of the deductions under clauses (a) to (h) above; and

(j) the actual cost paid by AstraZeneca, its Affiliates or its or their Sublicensees for each unit of a Device.

Net Sales (including any deductions) will be calculated using AstraZeneca's internal audited systems used to report such sales as adjusted for any of the items above not taken into account in such systems, and in each case which are in accordance with AstraZeneca's Accounting Standards, fairly applied and as employed on a consistent basis throughout AstraZeneca's operations. To the extent any accrued amounts used in the calculation of Net Sales are estimates, such estimates shall be trued-up to actuals in accordance with AstraZeneca's Accounting Standards (including that, for any estimates of deductions that are later decreased, the difference will be added back to Net Sales). Deductions pursuant to subsection (d) above will be taken in the Calendar Quarter in which such sales are no longer recorded as a receivable. As used above, the term "Device" means any device approved by a Regulatory Authority for use with the Licensed Product that is necessary to administer the Licensed Product to a patient (*i.e.*, without such device the Licensed Product cannot be delivered in accordance with the Regulatory Approval).

1.157 "***Non-Breaching Party***" has the meaning set forth in Section 16.2.1(a).

1.158 "***Non-Reimbursable Expenses***" means each of the following, except as expressly included in Eligible Expenses (or a category of expenses included therein) or unless otherwise mutually agreed by the Parties:

(a) the upfront fees payable by AstraZeneca to Akcea pursuant to Section 11.1;

(b) the milestone payments payable by AstraZeneca to Akcea pursuant to Section 11.2 and Section 11.3;

(c) any royalties payable by AstraZeneca to Akcea pursuant to Section 11.5 and Section 11.6;

(d) expenses associated with stock-based compensation expenses; and

(e) any amounts deducted from gross sales for the purpose of calculating Net Sales.

1.159 "***Non-Transferring Party***" has the meaning set forth in Section 17.3.

1.160 "***Notice of Intent***" has the meaning set forth in Section 9.1.

1.161 "***Opt-Out Date***" has the meaning set forth in Section 3.6.2(a).

1.162 "***Opt-Out Right***" has the meaning set forth in Section 3.6.1.

1.163 "***Opt-Out Scenario One Royalties***" has the meaning set forth in Section 3.6.2(b)(i).

1.164 "***Opt-Out Scenario One Royalty Rates***" has the meaning set forth in Section 3.6.2(b)(i).

1.165 "***Order***" means any writ, judgment, order, decree, injunction, award or ruling of any Governmental Authority.

1.166 "***Other Operating Expenses***" means the following FTE Costs and Out-of-Pocket Costs incurred after the Closing Date, to the extent, unless specifically stated otherwise, reasonably allocable to the Exploitation of the Licensed Product in the U.S. after the Closing Date and prior to the Opt-Out Date:

(a) [***];

(b) [***];

(c) [***];

(d) [***];

(e) [***];

(f) [***];

(g) any other categories of expenses included in the Development Plan and Budget, U.S. Medical Affairs Plan and Budget or U.S. Commercialization Plan and Budget for activities performed pursuant to the applicable plan for the Licensed Product but not accounted for in the definitions of Eligible Development Expenses, Eligible Medical Affairs Expenses, or Eligible Commercialization Expenses; and

(h) other expenses incurred by or on behalf of a Party or its Affiliates in connection with the Exploitation of such Licensed Product approved by the JSC as Other Operating Expenses.

No expense included as an Eligible Development Expense, an Eligible Commercialization Expense or an Eligible Medical Affairs Expense will also be included as an Other Operating Expense.

1.167 "***Other Operating Expenses Cost Share Notice***" has the meaning set forth in Section 11.10.2.

1.168 "[***]" means costs incurred by a Party or for its account that are attributable to [***].

1.169 "***Out-of-Pocket Costs***" means, with respect to a Party, costs and expenses actually paid by such Party or its Affiliates to Third Parties (or payable to Third Parties and accrued in accordance with such Party's Accounting Standards), other than employees of such Party or its Affiliates; *provided* that Out-of-Pocket Costs shall not include any costs that are subsumed within the definition of Included FTE Costs and Expenses.

1.170 "***Party***" or "***Parties***" has the meaning set forth in the Preamble of this Agreement.

1.171 "***Party Affiliate***" has the meaning set forth in the definition of "*Control*."

1.172 "***Party Vote***" has the meaning set forth in Section 6.6.1.

1.173 "***Patent Challenge***" has the meaning set forth in Section 16.2.3.

1.174 "***Patent Costs***" means the Out-of-Pocket Costs paid to outside legal counsel and other Third Parties incurred (a) in the Prosecution and Maintenance of Akcea Product-Specific Patents or AstraZeneca Patent Rights claiming: (i) the specific composition of matter of a Licensed Compound or a Licensed Product, or (ii) methods of using a Licensed Compound or a Licensed Product as a prophylactic, therapeutic or diagnostic, or (b) in challenging any Patent Right Controlled by Third Parties to obtain freedom to operate for a Licensed Product, in each case ((a) and (b)), with respect to the U.S.

1.175 "***Patent Right***" means (a) issued patents, patent applications, inventor's certificates and similar government-issued rights protecting inventions in any country or jurisdiction however denominated, (b) all priority applications, provisionals, 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 patents-of-additions, registrations, reissues, renewals, re-examinations, confirmations, supplementary protection certificates, and extensions or restorations mechanisms, including patent term adjustments, pediatric exclusivity, Patent Term Extensions or the equivalent thereof of any of (a), (b), or (c) and (d) United States and foreign counterparts of any of the foregoing.

1.176 "***Patent Term Extensions***" means any and all extensions of a term of a Patent Right granted under the patent Laws of any country in the Territory, including supplementary protection certificates, patent term linkages and any other extensions that are now or in the future become available, wherever applicable.

1.177 "***Permitted Licenses***" means (a) licenses granted by Akcea or its Affiliates under the Akcea Core Technology Patent Rights, the Akcea Core Technology Know-How, the Akcea Manufacturing Patent Rights, or the Akcea Manufacturing and Analytical Know-How (but not under the Akcea Product-Specific Patent Rights or the Akcea Product-Specific Know-How) to enable such Third Party to manufacture or formulate oligonucleotides generally (and not specific to TTR), where (i) such Third Party is primarily engaged in providing contract manufacturing or services and is not engaged in drug discovery, development or commercialization of therapeutics in any material respect; and (ii) Akcea and its Affiliates do not assist such Third Party, or grant rights to such Third Party, to identify, discover or make an antisense oligonucleotide designed to bind to TTR; and (b) material transfer, collaboration, or sponsored research agreements with academic collaborators or non-profit institutions solely to conduct non-commercial research, in each case in this clause (b), to the extent [***].

1.178 "***Person***" means any individual, firm, corporation, partnership, limited liability company, trust, business trust, joint venture company, Governmental Authority, association or other entity.

1.179 "***Phase 1 Clinical Trial***" means a human clinical trial (or a portion of a human clinical trial) of a product in any country, the principal purpose of which is a preliminary determination of safety in healthy individuals or patients, that would satisfy the requirements of 21 C.F.R. 312.21(a), or a similar clinical study prescribed by the relevant Regulatory Authorities in a country other than the United States.

1.180 "***Phase 2 Clinical Trial***" means a human clinical trial (or a portion of a human clinical trial) of a product in any country that would satisfy the requirements of 21 C.F.R. 312.21(b) and whose design is intended to explore a variety of doses, dose response, and duration of effect, and to generate initial evidence of clinical safety and activity in a target patient population, or a similar clinical study prescribed by the relevant Regulatory Authorities in a country other than the United States.

1.181 "***Phase 3 Clinical Trial***" means (a) a human clinical trial (or a portion of a human clinical trial) of a product in any country that would satisfy the requirements of 21 C.F.R. 312.21(c) and whose design is intended to (i) establish that the product is safe and efficacious for its intended use, (ii) define warnings, precautions and adverse reactions that are associated with the product in the dosage range to be prescribed, and (iii) support Regulatory Approval for such product, or (b) such other Clinical Trial designated as a Phase 3 Clinical Trial in the Development Plan and Budget, the protocol for such trial, or on clinicaltrials.gov (or foreign equivalent).

1.182 "***PN***" means transthyretin-mediated amyloid polyneuropathy. For the avoidance of doubt, PN includes polyneuropathy of wild-type or hereditary transthyretin-mediated amyloidosis.

1.183 "***Potential*** [***]" has the meaning set forth in Section 9.1.

1.184 "***Pricing and Reimbursement Approval***" means any approval, agreement, determination, or decision received from a Governmental Authority establishing prices that can be charged to consumers for a pharmaceutical product or that will be reimbursed by Governmental Authorities for a pharmaceutical product, in each case, in a country in the Territory where Governmental Authorities or Regulatory Authorities approve or determine pricing for pharmaceutical products for reimbursement or otherwise.

1.185 "***Prior Agreements***" means the agreements listed on Schedule 1.185 attached hereto, each, as in effect on the Execution Date, without further amendment, modification or supplement (subject to that certain Letter Agreement by and among AstraZeneca, Akcea and Ionis, dated as of the Execution Date).

1.186 "***Prosecution and Maintenance***" or "***Prosecute and Maintain***" means, with regard to a Patent Right, the preparation, filing, prosecution and maintenance of such Patent Right, as well as re-examinations, reissues, appeals, and requests for patent term adjustments and Patent Term Extensions with respect to such Patent Right, together with the initiation or defense of interferences, the initiation or defense of oppositions and other similar proceedings with respect to the particular Patent Right, and any appeals therefrom. For clarification, "***Prosecution and Maintenance***" or "***Prosecute and Maintain***" will not include any other enforcement actions taken with respect to a Patent Right.

1.187 "***PTC***" means PTC Therapeutics International Limited or its successors, assigns or designees under the PTC Agreement.

1.188 "***PTC Agreement***" means the Collaboration and License Agreement dated August 1, 2018, by and between PTC and Akcea.

1.189 "***PTC Territory***" means Latin America and the Caribbean, using the United Nations M49 standard definition for that region, but excluding the following countries and territories: Anguilla, Aruba, Bahamas, Barbados, Bonaire, Sint Eustatius and Saba, British Virgin Islands, Cayman Islands, Curaçao, Guadeloupe, Martinique, Montserrat, Puerto Rico, Saint Barthélemy, Saint Martin (French Part), Sint Maarten (Dutch part), Turks and Caicos Islands, United States Virgin Islands, Bouvet Island, Falkland Islands (Malvinas), French Guiana, South Georgia and the South Sandwich Islands.

1.190 "***PTC Territory License Date***" has the meaning set forth in Section 8.1.1.

1.191 "***Receiving Party***" has the meaning set forth in Section 13.1.

1.192 "***Reference Calendar Year***" has the meaning set forth in Section 3.2.3(b).

1.193 "***Reference Product***" has the meaning set forth in the definition of "*Generic Intrusion*".

1.194 "***Regulatory Approval***" means, with respect to a country or other jurisdiction in the Territory, the approval of the applicable Regulatory Authority necessary for the marketing and sale of a product in such country or other jurisdiction, including, where applicable, (a) Pricing and Reimbursement Approvals in such country or other jurisdiction and (b) the expansion or modification of the label for additional Indications or uses, but excluding any Emergency Use Approval pursuant to Section 564 of the United States Federal Food, Drug and Cosmetic Act, as amended, and any similar approval in a country other than the U.S.

1.195 "***Regulatory Approval Application***" means (a) an NDA, (b) an MAA or (c) any other application to seek Regulatory Approval of a product in any country in the Territory, as defined in applicable Laws and filed with the relevant Regulatory Authorities of such country.

1.196 "***Regulatory Authority***" means the FDA in the United States, or any Governmental Authority in another country that holds responsibility for granting Regulatory Approval for a product in such country and any successor(s) thereto.

1.197 "***Regulatory Exclusivity Period***" means, with respect to each Licensed Product in any country in the Territory, a period of exclusivity (other than Patent Right exclusivity) granted or afforded by applicable Law or by a Regulatory Authority in such country that confers exclusive marketing rights with respect to such Licensed Product for all approved Indications in such country, such as new chemical entity exclusivity, orphan drug exclusivity, non-patent related pediatric exclusivity or any other applicable marketing exclusivity, including any such periods listed in the FDA's Orange Book or any such periods under national implementations in the EU of Article 10 of Directive 2001/83/ED, Article 14(11) of Parliament and Council Regulation (EC) No. 726/2004, Parliament and Council Regulation (ED) No. 141/2000 on orphan medicines, Parliament and Council Regulation (ED) No. 1901/2006 on medicinal products for pediatric use and all international equivalents of any of the foregoing.

1.198 "***Regulatory Filing***" means, with respect to a product, any documentation comprising or relating to or supporting any filing or application with any Regulatory Authority with respect to such product, or its use or potential use, including any document submitted to any Regulatory Authority, including any IND, any drug master files, any Regulatory Approval Application and any correspondence with any Regulatory Authority with respect to such product (including minutes of any meetings, telephone conferences or discussions with any Regulatory Authority).

1.199 "***Regulatory Owner***" has the meaning set forth in Section 4.3.1.

1.200 "***Regulatory Strategy***" has the meaning set forth in Section 4.1.

1.201 "***Regulatory Working Group***" or "***RWG***" has the meaning set forth in Section 6.5.1.

1.202 "***Reversion License***" has the meaning set forth in Section 16.3.1(b)(i).

1.203 "***Right of First Negotiation***" has the meaning set forth in Section 9.1.

1.204 "***ROW Commercialization Plan***" has the meaning set forth in Section 3.3.

1.205 "***ROW Development Activities***" has the meaning set forth in Section 2.2.2.

1.206 "***ROW Net Sales***" has the meaning set forth in Section 11.6.1.

1.207 "***ROW Royalties***" has the meaning set forth in Section 11.6.1.

1.208 "***ROW Royalty Rates***" has the meaning set forth in Section 11.6.1.

1.209 "***ROW Territory***" means the Territory other than U.S.

1.210 "***Royalties***" means ROW Royalties and U.S. Royalties.

1.211 "***Royalty Term***" means, with respect to each Licensed Product in each country in the Territory, the period commencing on the First Commercial Sale of such Licensed Product in such country and expiring upon the latest of (a) [***], (b) [***], (c) [***], and (d) the [***] anniversary of the First Commercial Sale of such Licensed Product in such country.

1.212 "***SDEA***" has the meaning set forth in Section 4.6.2.

1.213 "***Second Opt-Out Period***" has the meaning set forth in Section 3.6.1.

1.214 "***Securities Acts***" means the Securities Act of 1933, as amended, the Securities Exchange Act of 1934, as amended, or any other applicable securities Law.

1.215 "***Senior Officers***" means the President of Akcea and the Executive Vice President for BioPharmaceuticals R&D or Executive Vice President for BioPharmaceuticals Commercial of AstraZeneca, or the functional successor in their respective organizations, or their respective designees at Senior Vice President level or above who have the authority to decide the applicable matter.

1.216 "***Settlement Sublicense***" means a sublicense to a Third Party granted by AstraZeneca under its licenses set forth in Section 8.1 to settle or avoid litigation related to (a) the alleged infringement by a Licensed Compound or Licensed Product or the Exploitation thereof of any Patent Rights or other intellectual property of a Third Party or (b) the alleged non-infringement, invalidity or unenforceability of any Patent Rights claiming a Licensed Compound or Licensed Product or Exploitation thereof; *provided* that any payments received from a Third Party under a Settlement Sublicense as consideration for the Settlement Sublicense will be shared as provided in Section 12.4.4.

1.217 "[***]" means, with respect to [***]; *provided* that if [***], then [***]:

Reference Calendar Year	[***] **for such Reference Calendar Year**
2022	[***]%
2023	[***]%
2024	[***]%
2025	[***]%
2026	[***]%
2027	[***]%
2028	[***]%
2029 and each Calendar Year thereafter	[***]%

1.218 "***Statement of Interest***" has the meaning set forth in Section 9.1.

1.219 "***Subcommittee***" has the meaning set forth in Section 6.2.

1.220 "***Sublicense***" has the meaning set forth in Section 8.4.

1.221 "***Sublicensee***" means a Third Party to whom AstraZeneca or its Affiliates has granted a Sublicense under any Licensed Technology in accordance with the terms and conditions of this Agreement. For clarity, Akcea and its Affiliates are not Sublicensees of AstraZeneca.

1.222 "***Supply Agreement***" means any agreement between AstraZeneca and a Third Party for the supply of the Licensed Compound or Licensed Product to AstraZeneca, but solely to the extent that any such agreement is solely and exclusively related to the Licensed Product and not any other AstraZeneca product.

1.223 "***Term***" has the meaning set forth in Section 16.1.

1.224 "***Terminated Territory***" means, with respect to a Licensed Product, any country or jurisdiction for which this Agreement is terminated with respect to such Licensed Product, or the Territory if this Agreement is terminated in its entirety with respect to such Licensed Product.

1.225 "***Territory***" means all countries of the world other than (a) the Terminated Territory and (b) the PTC Territory unless and until the PTC Territory License Date. For clarity, from and after the PTC Territory License Date, the "Territory" shall include the PTC Territory.

1.226 "***Third Party***" means any Person that is neither a Party nor an Affiliate of a Party.

1.227 "***Third Party Claims***" has the meaning set forth in Section 15.1.

1.228 "***Third Party Payments***" has the meaning set forth in Section 11.6.2(d).

1.229 "***Trademark***" means any word, name, symbol, color, shape, designation or any combination thereof, including any trademarks, service marks, certification marks, trade dress, internet domain names, trade names, identifying symbols, designs, product names, company names, slogans, logos or insignia, that functions as an identifier of source, origin or quality, whether registered or unregistered, and all common law rights, applications and registrations therefor, and all goodwill associated therewith, and all domain names, URLs or social media tags, handles and other identifiers containing such marks.

1.230 "***Transferring Party***" has the meaning set forth in Section 17.3.

1.231 "***Transition Period***" has the meaning set forth in Section 16.3.3(a)(iii).

1.232 "***Transition Plan***" has the meaning set forth in Section 16.3.3(a)(i).

1.233 "***Transition Services***" has the meaning set forth in Section 16.3.3(a)(i).

1.234 "***TTR***" means the human gene transthyretin (NCBI Accession No. NM_000371; Gen ID: 7276), or any alternative splice variants, mutants, polymorphisms and fragments thereof.

1.235 "***United States***" or "***U.S.***" means the United States of America and all of its territories and possessions.

1.236 "***U.S. Commercialization Plan and Budget***" has the meaning set forth in Section 3.2.1.

1.237 "***U.S. Development Activities***" has the meaning set forth in Section 2.4.1.

1.238 "***U.S. Medical Affairs Plan and Budget***" has the meaning set forth in Section 3.2.2.

1.239 "***U.S. Royalties***" has the meaning set forth in Section 11.5.1.

1.240 "***U.S. Royalty Rates***" has the meaning set forth in Section 11.5.1.

1.241 "***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.

Schedule 1.11

Akcea Core Technology Patent Rights

Akcea Docket Number	Country	Status	Patent/ Application No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]	[***]
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Akcea Docket Number	Country	Status	Patent/ Application No.	Filing Date	Grant Date	Title
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Akcea Docket Number	Country	Status	Patent/ Application No.	Filing Date	Grant Date	Title
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Schedule 1.18

Akcea Manufacturing Patent Rights

Technology	Akcea Docket Number	Status	Country/Treaty	Application/Patent Number	Filing Date	Title
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]
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Schedule 1.23

Akcea Product-Specific Patent Rights

Akcea Docket Number	Country	Status	Patent/ Application No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]		[***]
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Akcea Docket Number	Country	Status	Patent/ Application No.	Filing Date	Grant Date	Title
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Schedule 1.94

Existing In-License Agreements

1. [***]

2. Development, Commercialization and License Agreement between Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc. dated March 14, 2018 (subject to that certain Letter Agreement by and among between AstraZeneca AB, Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc., dated as of the Execution Date)

Schedule 1.185

Prior Agreements

1. [***]

2. Development, Commercialization and License Agreement between Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc. dated March 14, 2018 (subject to that certain Letter Agreement by and among between AstraZeneca AB, Akcea Therapeutics, Inc. and Ionis Pharmaceuticals, Inc., dated as of the Execution Date)

3. [***]

Schedule 2.2.1

Initial Development Plan and Budget

[***]

ION-682884 (Eplontersen)
INITIAL DEVELOPMENT PLAN[1]
December 6, 2021

The purpose of this document is to describe:

[***]

[1] To be updated after the Closing Date and approved by the Joint Steering Committee

1. INTRODUCTION

[***]

1.1. Key program goals to the end of Phase 3

[***]

2. NONCLINICAL DEVELOPMENT PLAN

2.1. Toxicology and Pharmacokinetic Studies

2.1.1.Toxicology and PK Summary

[***]

Table 1: Eplontersen Toxicology and Safety Pharmacology Studies.

Study Type and Duration (Study Number)	Species and Strain	Route	Dose and Regimen	GLP
Repeated-Dose Toxicity				
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
Genotoxicity				
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
Reproductive and Developmental Toxicity				
[***]	[***]	[***]	[***]	[***]
Carcinogenicity				
[***]	[***]	[***]	[***]	[***]
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[***]	[***]	[***]	[***]	[***]
Safety Pharmacology				
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]

[***]

2.1.2. Pharmacokinetic Summary

[***]

Table 2: Summary of eplontersen Pharmacokinetic Studies.

Study No.	Study Title	Dosing Route	Doses and Regimen	GLP
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
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[***]

2.2. Reproductive Toxicology Studies

[***]

2.3 Carcinogenicity Studies

[***]

Table 3: Key Dates for Mouse and Rat Carcinogenicity Studies.

Carc. Study	Start	End In-Life	Prelim. Data	Report
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]

Table 4: Planned Actions and Studies for Carcinogenicity Program.

Action	Completion Date
[***]	[***]
[***]	[***]
[***]	[***]

2.4 Impurity Qualification Study

[***]

Table 5: Key Dates for Mouse Impurity Qualification Study.

Qualification Study	Start	End In-Life	Prelim. Data*	Report
[***]	[***]	[***]	[***]	[***]

2.5 Immunogenicity Assessment (Anti-Drug Antibody Analysis)

[***]

Table 6: Key Dates for Immunogenicity Assessment for Preclinical Studies

IM Assessment	Start	End	Prelim. Data*	Report
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]

3. CLINICAL DEVELOPMENT PLAN

3.1. ION-682884-CS2: Phase 3

Figure 1: CARDIO-TTRansform Study Schema

[***]

3.2. ION-682884-CS3: Phase 3

[***]

3.3. ION-682884-CS20: Phase 1

[***]

3.3.1. Study Design

[***]

Table 7: Study ION-682884-CS20 Design and Current Extent of Exposure

Cohort	Dose Level	Doses	Total Dose	Subject N (Eplontersen: Placebo)
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]

[***]

Summary of results:

- [***]
- [***]
- [***]

3.4. ION-682884-CS21: Phase 1

[***]

3.4.1. Study Design

[***]

Primary Endpoint

[***]

Secondary Endpoint

[***]

3.4.2. Drug Interaction Studies

[***].

3.4.3. Immunogenicity Assessment (Anti-Drug Antibody Assessment)

[***]

[***]

Table 8: Key Dates for Immunogenicity Assessment

IM Assessment	Start	End	Prelim. Data*	Report
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]

3.4.4. Studies in Special Populations

[***]

3.4.5. 'Thorough QT' Study

[***]

Table 9: Key Dates for [***]

QT Assessment	Start	End	Prelim. Data*	Report
[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]

3.4.6. Human ADME Study

[***]

3.4.7. Population PK and PKPD Study

[***]

4. REGULATORY STRATEGY

[***]

5. MANUFACTURING STRATEGY

[***]

6. ROLES AND RESPONSIBILITIES

[***]	[***]	[***]
[***]	[***]	[***]
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7. BUDGET

[***]

8. DEVELOPMENT PLAN

[***]

Schedule 3.2.1

Allocation of Co-Commercialization and Medical Affairs Activities

[***]

Function		Responsible Party	Activities	
Patient Management Functions				
			Global	**US**
[***]		[***]	[***]	[***]
		[***]	[***]	[***]
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Customer-Facing Functions				
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Schedule 3.2.3(b)

Cost Share Scenarios

US COMMERCIAL/MEDICAL AFFAIRS BUDGET EXAMPLE
[***]

[***]	[***]						
	[***]	[***]	[***]	[***]	[***]	[***]	[***]
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Schedule 6.8

Alliance Manager Activities

Each Alliance Manager is responsible for:

(a) Promoting the overall health of the relationship between the Parties;

(b) Organizing each meeting of the Parties, including agendas, drafting minutes, and publishing final minutes; and

(c) Assisting the JDC and JCMC in preparing status and progress reports on the above as determined necessary by the Parties.

Schedule 7.2.2

Existing Third Party Subcontractors

[***]

Schedule 8.3.2

Authorized CMOs as of the Execution Date

[***]

Schedule 16.3.3(a)(ii)

Transition Plan Dispute Resolution

[***]

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Akcea Therapeutics, Inc., a Delaware Corporation

Akcea Therapeutics Canada Inc., a Canadian Corporation

Akcea Therapeutics France SAS, a French Company

Akcea Therapeutics Germany GmbH, a German Corporation

Akcea Therapeutics UK Limited, a United Kingdom Limited Private Company

Akcea Securities Corporation., a Massachusetts Corporation

Akcea Therapeutics Ireland Limited, an Irish Private Company

Isis USA Limited, a United Kingdom Limited Private Company

Osprey Therapeutics, Inc., a Delaware Corporation

PerIsis I Development Corporation, a Delaware Corporation*

Symphony GenIsis, Inc., a Delaware Corporation*

Ionis Development (Ireland) Limited, an Irish Private Company

* PerIsis I Development Corporation and Symphony GenIsis, Inc. were dissolved in September 2021.

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements on Form S-3 (Nos. 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447, 333-151076, 333-188407, 333-217422 and 333-242382) and in the related Prospectuses, as applicable, and in the Registration Statements on Form S-8 (Nos.333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853, 333-142777, 333-151996, 333-160269, 333-168674, 333-176136, 333-184788, 333-190408, 333-207900, 333-219801, 333-233143, 333-242386, 333-251855, and 333-258503) of Ionis Pharmaceuticals, Inc. of our reports dated February 24, 2022, with respect to the consolidated financial statements of Ionis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Ionis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2021.

/s/ ERNST & YOUNG LLP

San Diego, California
February 24, 2022

Exhibit 31.1

CERTIFICATION

I, Brett P. Monia, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: February 24, 2022

/s/ BRETT P. MONIA

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

Exhibit 31.2

CERTIFICATION

I, Elizabeth L. Hougen, certify that:

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

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

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

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

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

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

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

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

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

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

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

Dated: February 24, 2022

/s/ ELIZABETH L. HOUGEN

Elizabeth L. Hougen
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

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

1. The Company's Annual Report on Form 10-K for the year ended December 31, 2021, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: February 24, 2022

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

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

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

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