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, 2023

☐ **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 Exchange 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 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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 $4,243,321,410 as of June 30, 2023.*

The number of shares of voting common stock outstanding as of February 15, 2024 was 145,751,797.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive Proxy Statement to be filed on or about April 25, 2024 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on June 6, 2024 are incorporated by reference into Part III of this Report.

* Excludes 39,747,443 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, 2023. 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 our commercial medicines, additional medicines in development and technologies. 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 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. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. 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":

- Our ability to generate substantial revenue from the sale of our medicines;
- The availability of adequate coverage and payment rates for our medicines;
- Our and our partners' ability to compete effectively;
- 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;
- Our ability to maintain the effectiveness of our personnel; and
- The impacts of pandemics, climate change, wars and other global events.

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.

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 practicable after we file such materials with, or furnish such materials to, 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, and other information that we file electronically with the SEC.

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2023
Table of Contents

PART I
Item 1. Business

Overview

For three decades as a pioneer in RNA-targeted medicines, we have focused on bringing better futures to people with serious diseases. Today, we continue to drive innovation in RNA therapies. A deep understanding of disease biology and an industry-leading drug discovery technology propels our work, coupled with a passion and urgency to deliver better futures for patients.

We currently have five marketed medicines to treat serious diseases: SPINRAZA (nusinersen), QALSODY (tofersen), WAINUA (eplontersen), TEGSEDI (inotersen) and WAYLIVRA (volanesorsen). We also have a rich innovative late- and mid-stage pipeline in neurology, cardiology and other areas of high patient need. We currently have nine medicines in Phase 3 development and multiple additional medicines in early and mid-stage development.

Over the past year, we made important progress executing on our vision to bring next-level value to patients and all stakeholders. We achieved this progress by focusing on a clear vision to prioritize and expand the Ionis wholly owned pipeline, deliver Ionis medicines directly to patients and enhance our technology leadership, all underscored by continued financial strength and responsibility. The United States, or U.S., Food and Drug Administration, or FDA, approved two Ionis-discovered medicines, QALSODY and WAINUA. We delivered positive Phase 3 data readouts for WAINUA, olezarsen and donidalorsen. Our Phase 3 pipeline expanded with study starts for bepirovirsen, IONIS-FB-L_{Rx} and zilganersen and we reported five additional positive data readouts from our mid- and late-stage pipeline. Our recent achievements position us to continue to deliver a steady cadence of potentially transformational medicines to patients in need in the near and mid-term. We also advanced our go-to-market plans for our near-term commercial opportunities, WAINUA, olezarsen and donidalorsen. And we expanded and diversified our technology when we advanced our first cardiac myocyte targeting medicine and medicines using our mesyl phosphoramidate, or MsPA, backbone into preclinical development.

We accomplished all of this while earning revenues of $788 million for 2023 and ending the year with a cash and short-term investment balance of $2.3 billion. Our multiple sources of revenue and capital structure enable us to continue investing in our commercial readiness efforts for multiple late-stage programs, our innovative pipeline and our technology. By continuing to focus on these priorities, we believe we are well positioned to drive future growth and to bring next-level value to patients and shareholders.

Marketed Medicines

SPINRAZA is the global market leader for the treatment of patients with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Our partner, Biogen, is responsible for commercializing SPINRAZA worldwide. From inception through December 31, 2023, we have earned more than $2.1 billion in revenues from our SPINRAZA collaboration, including more than $1.6 billion in royalties on sales of SPINRAZA.

QALSODY is an antisense medicine that received accelerated approval in April 2023 from the FDA for the treatment of adult patients with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS, a rare, neurodegenerative disorder that causes progressive loss of motor neurons leading to death. Our partner, Biogen, is responsible for commercializing QALSODY worldwide. The European Medicines Agency, or EMA, is currently reviewing QALSODY for approval in the European Union, or EU.

WAINUA is a once monthly, self-administered subcutaneous LIgand-Conjugated Antisense, or LICA, medicine that received FDA approval in December 2023 for the treatment of adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis, or ATTRv-PN, a debilitating, progressive, and fatal disease. WAINUA is the only approved medicine for the treatment of ATTRv-PN that can be self-administered via an auto-injector. We and AstraZeneca are commercializing WAINUA in the U.S. with the launch having commenced in January 2024. We and AstraZeneca are seeking regulatory approval for WAINUA in Europe and other parts of the world. AstraZeneca has exclusive rights to commercialize WAINUA outside of the U.S.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with ATTRv-PN. We sell TEGSEDI in the U.S. and Canada (collectively, North America) and Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or Sobi. In October 2023, our agreement for TEGSEDI in North America was terminated. As a result, Sobi is transitioning responsibilities to us. In February 2024, we began the process to withdraw the TEGSEDI New Drug Application, or NDA. 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 approved in Europe and Brazil as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. We sell WAYLIVRA in Europe through our distribution agreement with Sobi. In Latin America, PTC is commercializing WAYLIVRA in Brazil for two indications, FCS and familial partial lipodystrophy, or FPL, and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

Medicines in Registration and Phase 3 Studies

We currently have nine medicines in registration or Phase 3 studies for eleven indications, which are:

WAINUA (eplontersen) is our medicine to treat patients with transthyretin amyloidosis, or ATTR, that is approved in the U.S. for the treatment of adults with ATTRv-PN, under regulatory review in other countries for ATTRv-PN and in development for ATTR cardiomyopathy, or ATTR-CM. In September 2023, *The Journal of the American Medical Association*, or *JAMA*, published positive results from the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN showing WAINUA halted disease progression and continuously improved quality of life at 35-, 66- and 85-week analyses. In July 2023, we completed enrollment of the Phase 3 CARDIO-TTRansform study of WAINUA in patients with ATTR-CM with data planned for as early as 2025. In February 2024, the FDA granted Fast Track designation to WAINUA for the treatment of patients with ATTR-CM. Additionally, in January 2022 and October 2023, the FDA and EMA, respectively, granted orphan drug designation to WAINUA for the treatment of ATTR.

Olezarsen is our medicine in development for FCS, an ultra-rare indication and severe hypertriglyceridemia, or SHTG, a much broader indication. In September 2023, we reported positive results from the Phase 3 Balance study in patients with FCS showing statistically significant triglyceride lowering and a substantial reduction in acute pancreatitis events in addition to a favorable safety and tolerability profile. Based on our positive Phase 3 results in FCS patients we are preparing regulatory submissions to the FDA and EMA. In January 2023, the FDA granted fast track designation to olezarsen for the treatment of patients with FCS. Additionally, we are currently conducting a broad Phase 3 development program for olezarsen for the treatment of SHTG including three Phase 3 studies supporting development (CORE, CORE2 and ESSENCE). In February 2024, the FDA granted Breakthrough Therapy designation and orphan drug designation to olezarsen for the treatment of FCS. Additionally, in January 2023, the FDA granted olezarsen Fast Track designation for the treatment of patients with FCS.

Donidalorsen is our medicine in development for hereditary angioedema, or HAE. In January 2024, we reported positive data from the Phase 3 OASIS-HAE study in patients treated every four weeks or patients treated every eight weeks. We are currently conducting OASIS-Plus, our open-label study in patients who were either previously treated with other prophylactic therapies or who have completed OASIS-HAE. Throughout 2022 and 2023, we reported positive data from the Phase 2 study and Phase 2 open-label extension, or OLE, study, including two-year OLE data. In December 2023, we licensed European commercialization rights of donidalorsen to Otsuka Pharmaceutical Co., Ltd., or Otsuka. We are preparing to submit an NDA to the FDA. Otsuka is preparing to submit a Marketing Authorization Application, or MAA, to the EMA. In September 2023 and February 2024, the FDA and EMA, respectively, granted orphan drug designation to donidalorsen.

Zilganersen is our medicine in development for Alexander disease, or AxD. In September 2023, we advanced zilganersen into the Phase 3 portion of its ongoing study for patients with AxD. In September 2020 and October 2019, the FDA and EMA, respectively, granted orphan drug designation to zilganersen. Additionally in August 2020, the FDA granted rare pediatric designation to zilganersen.

Ulefnersen is our medicine in development for amyotrophic lateral sclerosis, or ALS, with mutations in the fused in sarcoma gene, or *FUS*. We are currently conducting a Phase 3 study of ulefnersen in juvenile and adult patients with FUS-ALS. In August 2023 and September 2023, the FDA and EMA, respectively, granted orphan drug designation to ulefnersen.

QALSODY (tofersen) is our medicine to treat patients with SOD1-ALS. In April 2023, the FDA granted Biogen accelerated approval of QALSODY for patients with SOD1-ALS. QALSODY is currently under regulatory review in the EU. Additionally, Biogen is developing QALSODY to treat presymptomatic SOD1-ALS patients in the ongoing ATLAS study. In September 2016 and August 2016, the FDA and EMA, respectively, granted orphan drug designation to QALSODY.

Pelacarsen is our medicine in development to treat patients with elevated lipoprotein(a), or Lp(a)-driven cardiovascular disease, or CVD. Novartis is developing pelacarsen, including conducting the ongoing Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with elevated Lp(a)-driven CVD, which achieved full enrollment in July 2022 with more than 8,000 patients. In April 2020, the FDA granted Fast Track designation to pelacarsen.

Bepirovirsen is our medicine in development for chronic hepatitis B virus, or HBV. GSK is developing bepirovirsen, including conducting the ongoing B-Well Phase 3 program in patients with HBV. GSK reported positive results from Phase 2 studies in 2023, including durable response data from the Phase 2 B-Sure long-term follow-up study of bepirovirsen in complete responder patients from the Phase 2b B-Clear study of patients with HBV. In February 2024, the FDA granted Fast Track designation to bepirovirsen.

IONIS-FB-L_{Rx} is our medicine in development for immunoglobulin A, or IgA, nephropathy, or IgAN, and geographic atrophy, or GA. In the second quarter of 2023, Roche advanced IONIS-FB-L_{Rx} into Phase 3 development in patients with IgAN. In October 2023, we reported positive interim data from the ongoing Phase 2 study of IONIS-FB-L_{Rx} in patients with IgAN. Additionally, IONIS-FB-L_{Rx} is in an ongoing Phase 2 study in patients with GA, refer to the IONIS-FB-L_{Rx} description below for further details.

Our Marketed Medicines –Bringing Value to Patients Today

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

SPINRAZA is the global market leader for the treatment of patients with SMA, a progressive, debilitating and often fatal genetic disease. Our partner, Biogen, is responsible for commercializing SPINRAZA worldwide.

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, in untreated people the *SMN2* gene can only produce approximately 10% 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. This includes the following ongoing studies:

- DEVOTE: 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. In 2022, Biogen reported final data from Part A of the ongoing, three-part DEVOTE study. Results from Part A, an open-label safety evaluation period in children and teens with later-onset SMA, suggest that the higher dosing regimen of SPINRAZA leads to higher levels of the drug in the cerebrospinal fluid, or CSF, supporting further development of a higher dose of SPINRAZA. Additionally, the results indicated that SPINRAZA was generally well-tolerated.
- RESPOND: In the Phase 4 RESPOND study, Biogen is evaluating the benefit of SPINRAZA in infants and children with a suboptimal clinical response to the gene therapy, onasemnogene abeparvovec. In 2023, Biogen presented interim results from the RESPOND study that showed improved motor function in most participants treated with SPINRAZA following treatment with onasemnogene abeparvovec.
- ASCEND: In the Phase 3b ASCEND study, Biogen is evaluating the clinical outcomes and assessing the safety of a higher dose of SPINRAZA in children, teens and adults with later-onset SMA following treatment with 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 2022, Biogen reported new NURTURE study data, showing that early and sustained treatment with SPINRAZA helped participants to maintain and/or make progressive gains in motor function. These data showed that after 11 months of additional follow-up since the 2020 interim analysis, all children who were able to walk alone maintained this ability and one child gained the ability to walk alone, increasing the total percentage of study participants able to walk from 92% to 96%. Further, most children achieved motor milestones within age-appropriate timelines and no major motor milestones were lost. The safety of SPINRAZA over this extended follow-up period was consistent with previously reported findings.

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 OLE study for patients with SMA who participated in prior SPINRAZA studies.

QALSODY – QALSODY (tofersen) is an antisense medicine used to treat ALS in adults who have a mutation in the superoxide dismutase 1, or SOD1, gene, or SOD1-ALS. The FDA granted QALSODY accelerated approval based on reduction in plasma neurofilament light chain, or NfL, observed in patients treated with QALSODY. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

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. It is estimated that there are approximately 1,400 patients with SOD1-ALS in the G7 countries (comprised of Canada, France, Germany, Italy, Japan, the United Kingdom and the U.S.).

Biogen is also evaluating QALSODY for treatment of presymptomatic individuals who have a SOD1 genetic mutation. See the "Tofersen" description under "Our Phase 3 Pipeline" section below for further information on the development program for presymptomatic individuals. Tofersen is one of three medicines we have in development to treat ALS.

QALSODY received accelerated approval from the U.S. FDA in April 2023 and is currently under regulatory review in the EU. The QALSODY NDA and MAA included results from a Phase 1 study in healthy volunteers, a Phase 1/2 study evaluating ascending dose levels, the Phase 3 VALOR study, and the Phase 3 OLE study, as well as 12-month integrated results from the Phase 3 VALOR study and the Phase 3 OLE study. The 12-month integrated data show that earlier initiation of QALSODY, compared to delayed initiation, slowed declines in clinical function, respiratory function, muscle strength and quality of life and build on the results previously observed in the initial readout. The 12-month data compare patients with early initiation of QALSODY (at the start of VALOR) to those who had a delayed initiation of QALSODY (six months later, in the OLE).

At the time of the 12-month analysis, because the majority of participants survived without permanent ventilation, the median time to death or permanent ventilation, could not be estimated. However, early survival data suggest a lower risk of death or permanent ventilation with earlier initiation of QALSODY. Additionally, the latest 12-month results showed that reductions in total SOD1 protein (a marker of target engagement) and neurofilament (a marker of axonal injury and neurodegeneration) were sustained over time. QALSODY reduced total CSF SOD1 protein and plasma neurofilament levels in both early- and delayed-start groups as follows:

- 33% and 21% reduction in SOD1 protein, the intended target for QALSODY, respectively
- 51% and 41% reduction in plasma neurofilament, a marker of neuron injury, respectively

QALSODY had a favorable safety and tolerability profile.

The FDA and EMA granted QALSODY orphan drug designation for the treatment of ALS in September 2016 and August 2016, respectively.

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

WAINUA – WAINUA (eplontersen) injection is a LICA medicine indicated for the treatment of adults with ATTRv-PN. WAINUA prevents the production of TTR protein, reducing the amount of amyloid buildup that damages organs and tissues. WAINUA was approved by the FDA in December 2023.

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.

ATTRv-PN is caused by the accumulation of misfolded mutated TTR protein in the peripheral nerves. Patients with ATTRv-PN 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 addressable patients, which includes those with ATTRv-PN and those with ATTRv- mixed phenotype worldwide.

Often, patients with ATTRv-PN will have TTR build up in the heart and experience cardiomyopathy symptoms. Similarly, patients with ATTR-CM may often have TTR build up in their peripheral nerves and experience nerve damage and a variety of symptoms, including progressive difficulty with motor functions. As a result, we are developing WAINUA to treat all types of ATTR. See the "WAINUA" description under "Our Phase 3 Pipeline" section below for further information on our development program for ATTR-CM.

FDA approval was based on the interim analysis of the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN. NEURO-TTRansform was a global, multi-center, randomized, open-label study designed to evaluate the efficacy, safety and tolerability of WAINUA. The study compared WAINUA to the historical placebo arm from the TEGSEDI (inotersen) NEURO-TTR Phase 3 study. In the interim analysis, WAINUA demonstrated a statistically significant and clinically meaningful change from baseline for the co-primary and secondary endpoints at 35 weeks compared to the external placebo group. In the study, WAINUA achieved an 81% ($p<0.0001$) least squares, or LS, mean reduction in the co-primary endpoint of serum TTR concentration compared to baseline, demonstrating reduced TTR protein production. WAINUA also demonstrated a significant treatment effect on the co-primary endpoint of modified Neuropathy Impairment Score +7, or mNIS+7, a measure of neuropathic disease progression, with a statistically significant difference in mean change from baseline versus the external placebo group ($p<0.0001$). The study also met its key secondary endpoint of change from baseline in the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy, or Norfolk QoL-DN, showing that treatment with WAINUA significantly improved patient-reported quality of life compared to the external placebo group ($p<0.0001$). In September 2023, The *Journal of American Medical Association, or JAMA,* published the Phase 3 NEURO-TTRansform study results.

Additionally, in April 2023, we presented positive data that WAINUA met all co-primary and secondary endpoints in the NEURO-TTRansform study at the final analysis at week 66. At week 66:

- WAINUA achieved a LS mean reduction of 82% in serum TTR concentration from baseline, compared to an 11% reduction from baseline in the external placebo group ($p<0.0001$).
- WAINUA stopped disease progression as measured by mNIS+7 resulting in a 0.28 point LS mean increase compared to a 25.06 point increase for the external placebo group from baseline (24.8 point LS mean improvement; $p<0.0001$).
- WAINUA improved quality of life demonstrating a 5.5 point LS mean decrease (improvement) on the Norfolk QoL-DN, compared to a 14.2 point increase (worsening) in the external placebo group (19.7 point LS mean improvement; $p<0.0001$).

And in July 2023, we reported that WAINUA continued to halt neuropathy disease progression and improve quality of life in patients with ATTRv-PN through the end of treatment analysis at week 85.

WAINUA is currently under regulatory review in the EU and other countries for the treatment of patients with ATTRv-PN.

In January 2022 and October 2023, the FDA and EMA, respectively, granted orphan drug designation to WAINUA for the treatment of ATTR.

In December 2021, we entered into an agreement with AstraZeneca to jointly develop and commercialize WAINUA in the U.S. We initially granted AstraZeneca exclusive rights to commercialize WAINUA outside the U.S., except for certain Latin American countries. In July 2023, we expanded those rights to include Latin America.

TEGSEDI – TEGSEDI (inotersen) injection is an antisense medicine indicated for the treatment of ATTRv-PN in adults. TEGSEDI prevents the production of TTR protein, reducing the amount of amyloid buildup that damages organs and tissues.

TEGSEDI is commercially available in numerous countries, including the U.S., many European countries, Canada, and Latin America. We launched TEGSEDI in the U.S. and EU in late 2018. In 2021, we began selling TEGSEDI in the U.S., Canada and Europe through our distribution agreement with Sobi. Refer to the section titled, *Overview*, for further details on our distribution agreement with Sobi. In Latin America, PTC is commercializing TEGSEDI in Brazil and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

The approvals of TEGSEDI were based on efficacy and safety data from the Phase 3 NEURO-TTR study in patients with ATTRv-PN.

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 acute, potentially fatal 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 one to two individuals per million and characterized by extremely elevated triglyceride levels, typically greater than 1,000 mg/dl. 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.

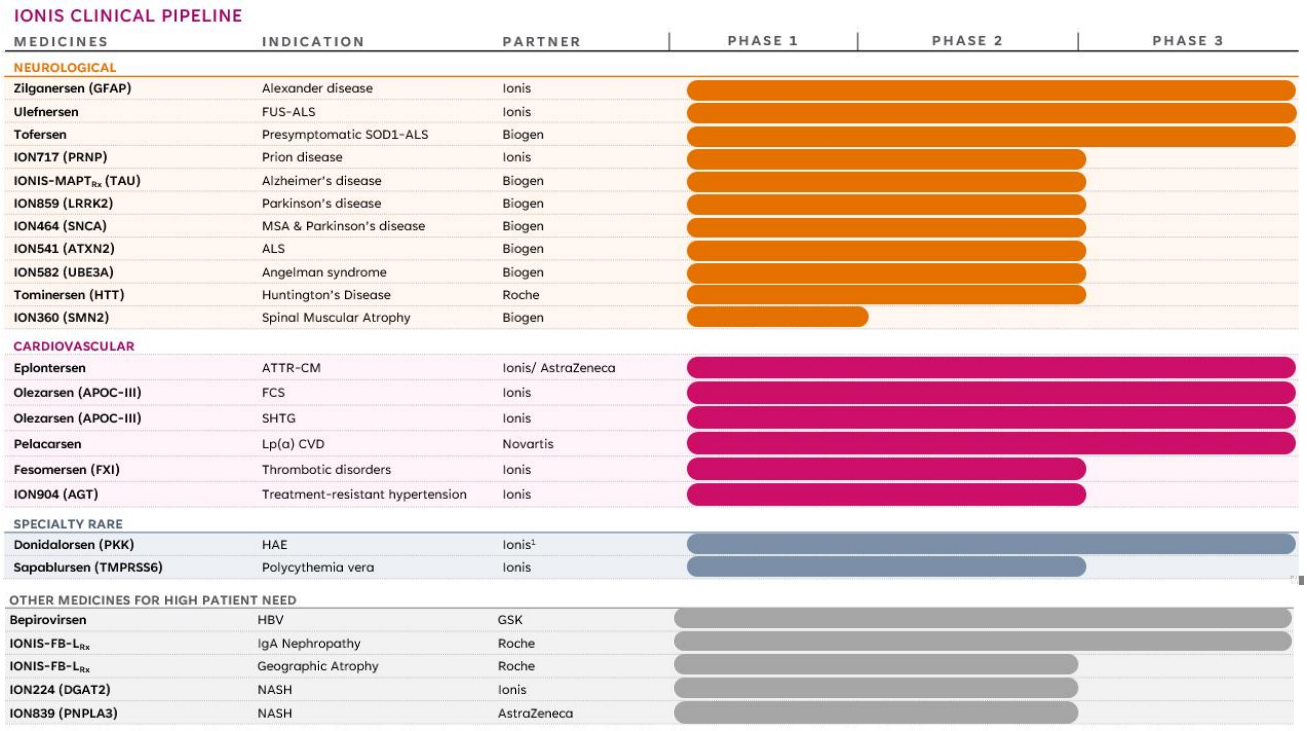
WAYLIVRA received conditional marketing authorization in May 2019 from the European Commission, or EC. WAYLIVRA is commercially available in multiple European countries and in Latin America. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA in Europe through our distribution agreement with Sobi. In Latin America, WAYLIVRA is approved for two indications, FCS and FPL. PTC is commercializing WAYLIVRA in Brazil and is pursuing access in additional Latin American countries through its exclusive license agreement with us. In the fourth quarter of 2022, WAYLIVRA was approved in Brazil for a second indication, FPL.

WAYLIVRA's conditional marketing authorization in the EU for FCS and approval in Brazil for FCS were based on efficacy and safety data from the Phase 3 APPROACH study and supported by results from the Phase 3 COMPASS study. WAYLIVRA's approval in Brazil for FPL was based on efficacy and safety data from the Phase 3 BROADEN study in patients with FPL.

Our Innovative Pipeline of Investigational Medicines

As a pioneer in RNA-targeted therapeutics, we continue to drive innovation with a leading pipeline in neurology, cardiology and other areas of high patient need.

The table below lists the medicines in our clinical pipeline and includes the disease indication, the partner (if the medicine is partnered), and the development status of each medicine. We categorize first-in-patient studies to establish a medicine's safety profile as Phase 1/2 and in the table below these are listed in the Phase 2 column. Studies in patients that are designed to establish an investigational medicine's proof of concept and additional safety profile are also listed in Phase 2. Pivotal studies designed to enable registrational filing for marketing authorization are listed in Phase 3. We have included descriptions for each of our medicines in Phase 2 and Phase 3 development below.



1 Granted Otsuka exclusive rights to commercialize donidalorsen in Europe.

Our Phase 3 Pipeline

We currently have nine medicines in our Phase 3 pipeline:

1 Granted Otsuka exclusive rights to commercialize donidalorsen in Europe.

Eplontersen (TTR) – Eplontersen (TTR) – Eplontersen (formerly IONIS-TTR-L_{Rx}) is an investigational LICA medicine we designed to inhibit the production of TTR protein. As discussed above under "WAINUA" in our "Marketed Medicines" section, we are developing eplontersen as a monthly self-administered subcutaneous injection to treat all types of ATTR, including ATTR-CM.

ATTR-CM 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 three to five years from disease onset. ATTR-CM includes both the genetic and wild-type form of the disease. There are an estimated 300,000 to 500,000 patients with ATTR-CM worldwide.

Often, patients with ATTRv-PN will have TTR build up in the heart and experience cardiomyopathy symptoms. Similarly, patients with ATTR-CM may often have TTR build up in their peripheral nerves and experience nerve damage and a variety of symptoms, including progressive difficulty with motor functions.

In January 2020, we initiated the CARDIO-TTRansform Phase 3 cardiovascular outcome study of eplontersen in patients with ATTR-CM. CARDIO-TTRansform is a global, multi-center, randomized, double-blind, placebo-controlled study in approximately 1,400 patients with ATTR-CM. We designed the study to evaluate the efficacy, safety and tolerability of eplontersen in patients with ATTR-CM. The primary endpoint in the CARDIO-TTRansform study is a composite outcome of cardiovascular mortality and recurrent cardiovascular clinical events up to Week 140. In July 2023, we announced that the CARDIO-TTRansform study had completed enrollment.

In January 2022 and October 2023, the FDA and EMA, respectively, granted orphan drug designation to WAINUA for the treatment of ATTR.

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 cardiovascular disease, or CVD. It is estimated that FCS affects one to two individuals per million worldwide and more than three million patients have SHTG in the U.S.

We are currently conducting a broad development program for olezarsen that includes the Phase 3 Balance study in patients with FCS and three Phase 3 studies supporting development for the treatment of SHTG: CORE, CORE2 and ESSENCE.

In September 2023, we reported positive topline data from the Phase 3 Balance study in patients with FCS. The study met its primary efficacy endpoint with a statistically significant reduction in triglyceride (TG) levels with the olezarsen 80 mg monthly dose at six months compared to placebo (p=0.0009); triglyceride lowering continued to improve at 12 months. In addition, olezarsen 80 mg showed a substantial reduction in acute pancreatitis events compared to placebo, a key secondary endpoint. Treatment with olezarsen 80 mg resulted in a >75% reduction in apoC-III, a protein produced in the liver that regulates TG metabolism in the blood. In addition to the 80 mg monthly dose, the study also evaluated a 50 mg monthly dose. Olezarsen demonstrated a dose-dependent effect, with both study doses showing a substantial reduction in acute pancreatitis compared to placebo. The 50 mg dose did not reach statistical significance at six months on the primary endpoint of triglyceride lowering (p=0.0775). Olezarsen demonstrated a favorable safety and tolerability profile in the study. Based on the positive results, we plan to file a New Drug Application, or NDA, in 2024 with the U.S. FDA in addition to EU regulatory filings for patients with FCS.

We are also conducting ongoing Phase 3 studies for the expanded SHTG patient population. CORE and CORE2 are global, multi-center, randomized, double-blind, placebo-controlled studies enrolling approximately 540 and 390 patients, respectively, designed to assess the efficacy, safety and tolerability of olezarsen in patients with SHTG. The CORE and CORE2 studies 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 studies is the percent change in fasting triglycerides from baseline at month six. Additionally, in November 2022, we initiated ESSENCE, a global, multi-center, randomized, double-blind, placebo-controlled study enrolling approximately 1,300 patients to provide a robust safety database. The primary endpoint of the study is the percent change in fasting triglycerides from baseline at month six.

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. Olezarsen also achieved statistical significance in numerous key secondary endpoints, including significant reductions in apoC-III. Olezarsen had a favorable safety and tolerability profile supportive of continued development.

In February 2024, the FDA granted Breakthrough Therapy designation and orphan drug designation to olezarsen for the treatment of FCS. Additionally, in January 2023, the FDA granted olezarsen Fast Track designation for the treatment of patients with FCS.

Donidalorsen (PKK) – Donidalorsen (formerly IONIS-PKK-L_{Rx}) is an investigational LICA medicine we designed to inhibit the production of prekallikrein, or PKK. HAE is a rare genetic disease that is characterized by severe and potentially fatal swelling of the arms, legs, face and throat. 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 HAE attacks. It is estimated that there are more than 20,000 patients with HAE in the U.S. and Europe.

In January 2024, we reported positive topline data from the Phase 3 OASIS-HAE study in patients with HAE. The study met its primary efficacy endpoint with a statistically significant reduction in the rate of HAE attacks in patients treated with 80 mg of donidalorsen via subcutaneous injection dosed every four weeks, or Q4W, (p<0.001) or every eight weeks, or Q8W, (p=0.004) compared to placebo. In addition, the trial showed donidalorsen achieved statistical significance on all secondary endpoints in the Q4W group and key secondary endpoints in the Q8W group. Donidalorsen demonstrated a favorable safety and tolerability profile in the study. Based on the positive results, we plan to file a NDA in 2024 with the U.S. FDA. Otsuka, which has exclusive rights to commercialize donidalorsen in Europe, is preparing to submit a Marketing Authorization Application to the European Medicines Agency, or EMA.

In May 2022, we initiated OASIS-Plus, a multi-center, open-label, global study in approximately 110 patients who were either previously treated with other prophylactic therapies or who have completed OASIS-HAE.

In 2021 and 2022 we reported positive results from the Phase 2 clinical study of donidalorsen in patients with HAE. And in 2022 and 2023, we presented positive results from the Phase 2 OLE study of donidalorsen in patients with HAE. Following the 13-week blinded, placebo-controlled Phase 2 study with a fixed 13-week dosing period where they received donidalorsen 80 mg every four weeks, patients were eligible for enrollment in the OLE study. Of the 20 Phase 2 study participants, 17 entered the OLE study and were on a fixed 13-week dosing period where they received 80 mg every four weeks. From week 17 through two years, patients entered a flexible dosing period where they either received donidalorsen 80 mg every four weeks, 80 mg every eight weeks, or 100 mg every four weeks. Over the two years, patients treated with donidalorsen via subcutaneous injection showed an overall sustained mean reduction in HAE attack rates of 96% from baseline, from 2.70 to 0.06 attacks per month, across all dosing groups. Furthermore, all patients treated with donidalorsen reported a clinically meaningful improvement in quality of life as measured by the Angioedema Quality of Life Questionnaire (AE-QoL) over two years. Donidalorsen had a favorable safety and tolerability profile in the study.

In September 2023 and February 2024, the FDA and EMA granted orphan drug designation to donidalorsen.

In December 2023, we granted Otsuka exclusive rights to commercialize donidalorsen in Europe.

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 CVD 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 it specifically targets the RNA that codes for all forms of the Apo(a) molecule. 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 are 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 July 2022, we announced that the Lp(a) HORIZON study had completed enrollment.

In November 2018, at the American Heart Association, or AHA, annual meeting, we reported results of the Phase 2 study of pelacarsen in patients with hyperlipoproteinemia(a). In the Phase 2 study, we observed statistically significant and dose dependent reductions from baseline in Lp(a) levels. Approximately 98% of patients who received the highest dose in the study demonstrated a reduction in Lp(a) levels to below the recommended threshold for CVD events (<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.

In April 2020, the FDA granted pelacarsen Fast Track designation for the treatment of patients with elevated Lp(a) and CVD. In December 2020, the Center for Drug Evaluation, or CDE, of China National Medical Products Administration granted breakthrough therapy designation to pelacarsen.

Zilganersen – Zilganersen (formerly ION373) is an investigational antisense medicine we designed to inhibit the production of glial fibrillary acidic protein, or GFAP. We are developing zilganersen as a potential therapy for AxD, 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 four 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 four 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 zilganersen in patients with AxD and in September 2023, we advanced zilganersen into the Phase 3 portion of the pivotal study. The pivotal study of zilganersen is a multi-center, double-blind, placebo-controlled, multiple-ascending dose study in approximately 55 patients with AxD designed to assess the efficacy, safety and tolerability of zilganersen. Patients will receive zilganersen or placebo for a 60-week period, after which all patients in the study will receive zilganersen for a 60-week open-label treatment period. The primary endpoint is the change from baseline in the 10-Meter Walk Test, or 10MWT.

In September 2020 and October 2019, the FDA and EMA, respectively, granted orphan drug designation to zilganersen. Additionally in August 2020, the FDA granted rare pediatric designation to zilganersen.

Ulefnersen (FUS) – Ulefnersen (formerly 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.

In April 2021, we initiated a Phase 3 study of ulefnersen in patients with FUS-ALS. The Phase 3 trial of ulefnersen is a global, multi-center, randomized, double-blind, placebo-controlled study in approximately 75 patients designed to assess the efficacy, safety and tolerability of ulefnersen. Part 1 of the trial consists of patients randomized to receive a loading regimen of ulefnersen or placebo for days one, 28 and 85 after which patients are dosed quarterly for a total of 61 weeks, followed by a 12 week follow up for participants entering Part 2 or 40 week follow up for participants not entering Part 2. Part 2 is an open-label period in which all patients in the trial will receive ulefnersen or placebo loading regimen at week four followed by one dose every 12 weeks for 85 weeks. The primary endpoint is the change from baseline as measured by joint rank analysis of the combined assessment of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, or 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.

In August 2023 and September 2023, the FDA and EMA, respectively, granted orphan drug designation to ulefnersen.

Tofersen (SOD1) (BIIB067) – Tofersen (formerly IONIS-SOD1$_{Rx}$) is an investigational antisense medicine we designed to inhibit the production of SOD1 protein, which is a well understood genetic cause of ALS. As discussed above under the "QALSODY" section in our "Marketed Medicines" section, Biogen is also evaluating tofersen for treatment of presymptomatic individuals who have a SOD1 genetic mutation.

In April 2021, Biogen initiated a Phase 3 study of tofersen, called ATLAS, in presymptomatic individuals with a SOD1 genetic mutation. ATLAS is a multi-center, randomized, double-blind, placebo-controlled study enrolling approximately 150 subjects designed to assess the efficacy, safety and tolerability of tofersen. Patients are only given tofersen if they meet a defined biomarker threshold or progress to develop clinically manifest SOD1-ALS.

In September 2016 and August 2016, the FDA and EMA, respectively, granted orphan drug designation to tofersen.

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.

Bepirovirsen (HBV) (GSK3228836) – Bepirovirsen (formerly IONIS-HBV$_{Rx}$) is an investigational antisense medicine we designed to inhibit the production of viral proteins associated with 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, affecting nearly 300 million people and resulting in approximately 900,000 deaths annually. 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.

In January 2023, GSK initiated the Phase 3 program of bepirovirsen, B-Well, in patients with chronic HBV. B-Well 1 and B-Well 2 are global, multi-center, randomized, double-blind, placebo-controlled studies enrolling more than 500 patients each. GSK designed these studies to assess the efficacy, safety and tolerability of bepirovirsen. The arms will be stratified based on HBsAg levels at screening. The primary endpoint is the number of patients achieving functional cure with baseline HBsAg ≤ 1,000 IU/mL. Functional cure is defined as a sustained suppression (24 weeks or longer) of HBV DNA (< Lower Limit of Quantification, or LLOQ) while off all HBV treatments with HBsAg loss (<0.05 IU/mL) with or without HBsAg after a finite duration of therapy.

In June 2022, GSK presented positive results from the Phase 2b B-CLEAR study of bepirovirsen in patients with chronic HBV infection. The end of study results showed that treatment with bepirovirsen in some patients resulted in sustained clearance of HBsAg and HBV DNA for 24 weeks after end of bepirovirsen treatment in people with chronic HBV infection. Treatment with bepirovirsen that was administered weekly at a dose of 300 mg per week for 24 weeks, with loading doses administered on day four and 11 (treatment arm 1), resulted in 9% of patients on NA treatment and 10% of patients not on NA treatment both achieving the primary outcome of HBsAg levels and HBV DNA levels below the LLOQ. This is defined as a sustained response and was observed for 24 weeks post last dose. Patients with low baseline HBsAg levels responded best to treatment with bepirovirsen with 16% and 25% of patients achieving the primary outcome in treatment arm one of the on NA and not on NA cohorts, respectively. Additionally in June 2023, GSK presented durable response data from the Phase 2 B-Sure long-term follow-up study of bepirovirsen in complete responder patients from the Phase 2b B-Clear study of patients with HBV. Bepirovirsen had a favorable safety and tolerability profile supportive of continued development.

In October 2023, GSK reported data from the B-Together Phase 2b study of bepirovirsen in patients with chronic HBV infection at the AASLD Liver Meeting. The data showed that between 9-15% of patients attained the primary outcome of HBsAg and HBV DNA below the LLOQ for 24 weeks after planned end of sequential treatment with pegylated interferon, in the absence of newly initiated antiviral therapy. Additionally, all patients who achieved the primary endpoint had a baseline HBsAg ≤3000 IU/mL. 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 results of the Phase 2a study of bepirovirsen in patients with chronic HBV infection. As a result, GSK is responsible for global development, regulatory and commercialization activities, and costs for the HBV program.

In February 2024, the FDA granted bepirovirsen Fast Track designation for the treatment of patients with chronic HBV infection.

IONIS-FB-L_{Rx} (IgAN) (RG6299) – IONIS-FB-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of complement factor B, or FB, and the alternative complement pathway. Genetic association studies have shown that overaction of the alternative complement pathway has been associated with the development of several complement-mediated diseases, including IgAN. As discussed below under the "IONIS-FB-L_{Rx}" section in our "Other Medicines in Development" section, we are also developing IONIS-FB-L_{Rx} for GA, secondary to 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 kidney failure. Also known as Berger's disease, IgAN is characterized by deposits of IgA in the kidneys, resulting in inflammation and tissue damage.

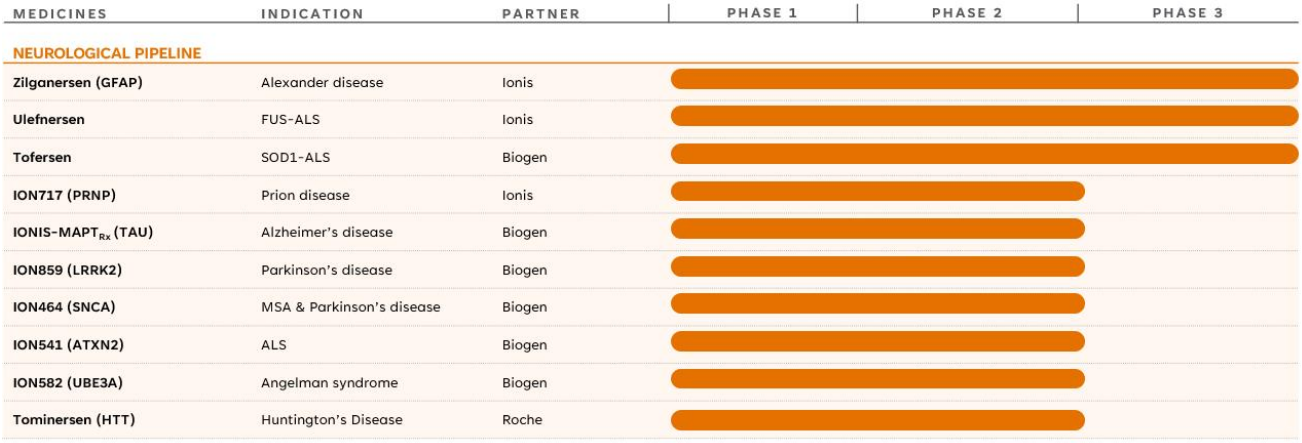
In April 2023, Roche initiated a Phase 3 study of IONIS-FB-L_{Rx}, called IMAGINATION, in patients with IgAN. IMAGINATION is a multi-center, randomized, double-blind, placebo-controlled study enrolling approximately 430 patients designed to assess the efficacy, safety and tolerability of IONIS-FB-L_{Rx}. The primary endpoint is the change from baseline in the urine protein-to-creatinine ratio, or UPCR, at week 37.

In November 2022, we presented positive results from the Phase 2 open-label study of IONIS-FB-L_{Rx} in patients with IgAN at the American Society of Nephrology's, or ASN, Kidney Week. In the Phase 2 study, which included results from the first 10 patients treated with IONIS-FB-L_{Rx}, IONIS-FB-L_{Rx} met its primary endpoint of change in 24-hour urinary protein, demonstrating a 44% mean reduction in proteinuria from baseline to week 29. Kidney function, as measured by estimated glomerular filtration rate, or eGFR, was maintained in all patients in the study. The results from the Phase 2 study provided proof-of-concept for the potential of IONIS-FB-L_{Rx} to treat patients with IgAN by inhibiting complement FB and the alternative complement pathway. Additionally, in November 2023 at ASN Kidney Week, we presented new positive interim results from the ongoing Phase 2 study, which included results from 13 patients. The results showed that IONIS-FB-L_{Rx} effectively and selectively reduced circulating FB, Alternate Pathway Activity, or AH50 and urinary complement Ba. Additionally, IONIS-FB-L_{Rx} reduced established proteinuria in patients with IgAN after six-months of treatment. The Phase 2 open-label study remains ongoing and will evaluate IONIS-FB-L_{Rx} in approximately 25 patients with IgAN. IONIS-FB-L_{Rx} had a favorable safety and tolerability profile supportive of continued development.

In July 2022, Roche exercised its option to license IONIS-FB-L_{Rx} following the positive Phase 2 results described above. As a result, Roche is responsible for global development, regulatory and commercialization activities, and costs for IONIS-FB-L_{Rx}, except for the open label Phase 2 study in patients with IgAN and the Phase 2 study in patients with GA, both of which we are conducting and funding.

Our Neurological Medicines in Development

We have a leading neurology franchise that includes three approved medicines for serious neurological diseases and a pipeline of investigational potential disease-modifying treatments for a broad range of neurological diseases. As we look to expand our wholly owned pipeline, we are focused on four pillars within our neurology franchise. We are first focusing on two areas: rare pediatric neurology and dementia, with plans to move into neuromuscular and peripheral neuropathies and motor diseases and then common neurological diseases in the future. We recently added ION717 for prion disease to our pipeline with plans to add three additional medicines by the end of 2024.



Zilganersen – See the medicine description under "Our Phase 3 Pipeline" section above.

Ulefnersen – See the medicine description under "Our Phase 3 Pipeline" section above.

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

ION717 (PRNP) – ION717 is an investigational antisense medicine we designed to inhibit the production of prion protein, or PrP, for the potential treatment of prion disease. Prion disease is a rare, fatal neurodegenerative disease caused by misfolding of PrP which accumulates in the brain. People with prion disease often experience progressive memory impairment, personality changes, difficulties with movement and loss of independence. There are currently no effective disease-modifying treatments for prion disease. In most cases, a person succumbs to prion disease within a year following symptom onset.

In December 2023, we initiated the Phase 1/2, PrProfile, study of ION717 in patients with prion disease. The current study is a randomized, multi-center, double-blind, placebo-controlled study in approximately 55 patients designed to assess the safety, tolerability and pharmacokinetics of multiple dose levels of ION717 administered intrathecally.

IONIS-MAPT$_{Rx}$ (TAU) (BIIB080) – IONIS-MAPT$_{Rx}$ is an investigational antisense medicine we designed to selectively inhibit production of the microtubule-associated protein tau (MAPT), or tau protein in the brain. We are developing IONIS-MAPT$_{Rx}$ to treat people with Alzheimer's disease, or AD.

AD is characterized predominantly by memory impairment and behavioral changes, resulting in a person's inability to independently perform daily activities. AD generally occurs late in life and may progress to death in five to 20 years after the onset of the disease.

In December 2022, Biogen initiated a Phase 2 clinical study of IONIS-MAPT$_{Rx}$ in patients with mild cognitive impairment or mild dementia due to AD. The study is a randomized, double-blinded, placebo-controlled, dose-escalation study in approximately 735 patients designed to assess the efficacy, safety and tolerability of IONIS-MAPT$_{Rx}$ administered intrathecally. The primary endpoint is the change from baseline to week 76 on the Clinical Dementia Rating scale Sum of Boxes, or CDR-SB.

In March 2023, Biogen presented new data from the Phase 1/2 study at the International Conference on Alzheimer's and Parkinson's Diseases. The data showed that IONIS-MAPT$_{Rx}$ reduced soluble tau protein in CSF in a dose-dependent and sustained manner in patients with early-stage AD. IONIS-MAPT$_{Rx}$ also reduced aggregated tau pathology, as measured by positron emission tomography, or PET, in all brain composites assessed. In October 2023, these data were published in *JAMA*. Additionally in October 2023, Biogen presented new data from the Phase 1/2 study at The Clinical Trials on Alzheimer's Disease, or CTAD, conference. The data showed a numerical difference favoring IONIS-MAPT$_{Rx}$ on multiple cognitive and functional scales for the patients receiving higher doses of IONIS-MAPT$_{Rx}$ throughout the multiple ascending dose and long-term extension compared to matched external control patients receiving placebo. The assessments included: Clinical Dementia Rating Sum of Boxes, or CDR-SB, Mini-Mental State Examination, or MMSE and, Functional Activities Questionnaire, or FAQ.

In July 2021, we and Biogen reported positive topline data from our Phase 1/2 study of IONIS-MAPT$_{Rx}$ in patients with mild AD at the Alzheimer's Association International Conference, or AAIC. The Phase 1/2 study was a blinded, randomized, placebo-controlled, dose-escalation study of IONIS-MAPT$_{Rx}$ to evaluate the safety and activity of once-monthly intrathecal injections of IONIS-MAPT$_{Rx}$ in patients with mild AD. The study showed that IONIS-MAPT$_{Rx}$ met its primary objective of safety and tolerability in patients with mild AD. The study demonstrated robust time and dose dependent lowering of tau protein in CSF over the three-month treatment period and sustained reductions during the six-month post-treatment period. 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$_{Rx}$. 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 are no approved disease modifying therapies.

In August 2019, Biogen initiated a Phase 1/2 study evaluating ION859 in patients with PD. The Phase 1/2 study is a global, multi-center, randomized, double-blinded, placebo-controlled study in approximately 80 patients 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 in approximately 40 patients designed to assess the safety and tolerability of multiple ascending 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 toxic aggregation of TDP-43, an RNA binding protein found in most patients with ALS, including the approximately 90% of the ALS population with no known family history of ALS.

In October 2020, Biogen initiated a Phase 1/2 clinical study evaluating ION541 in patients with ALS. The current study is a randomized, blinded, placebo-controlled study in approximately 110 patients 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 antisense 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. AS 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 are no approved disease modifying therapies.

In December 2021, we initiated the Phase 1/2 study, HALOS, of ION582 in patients with AS. The study is an open label dose-escalation study enrolling approximately 50 patients designed to assess the safety, tolerability and activity of multiple ascending doses of ION582 administered intrathecally. In November 2023, we announced that the HALOS study had completed enrollment.

In November 2023, we presented initial observations from the ongoing Phase 1/2 study at the Foundation for Angelman Syndrome, or FAST, summit. The data demonstrated that approximately 70% of patients showed a reduction in slow-wave electroencephalogram, or EEG, delta activity and over 80% showed an increase in faster frequency rhythms. Additionally, a majority of patients showed improvement in overall functioning on the SAS-CGI-C scale. A majority of patients also showed improvement on the total Bayley score, which is a direct assessment of clinical functioning.

In May 2022 and June 2022, the FDA and EMA, respectively, granted orphan drug designation to ION582. Additionally in July 2022 and May 2022, the FDA granted Fast Track designation and rare pediatric designation to ION582, respectively.

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 cytosine-adenine-guanine, or 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 2023, Roche initiated the Phase 2, GENERATION HD2, study of tominersen in patients aged 25 to 50 years old with prodromal and early manifest HD. The Phase 2 study of tominersen is a multi-center, double-blind, placebo-controlled study in approximately 360 patients designed to assess the efficacy, safety and tolerability of tominersen. Patients will receive tominersen or placebo every 16 weeks for 16 months, after which patients may receive tominersen in an open-label study. The primary endpoint is the change from baseline in the composite Unified Huntington's Disease Ratings Scale, or cUHDRS, (non-U.S.) and overall functional capacity, or TFC, (U.S.) at 16 months.

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. 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. In January 2022, Roche announced findings from a post-hoc analysis of the GENERATION HD1 study that suggested tominersen may benefit younger adult patients with lower disease burden.

In December 2015 and March 2015, the FDA and EMA, respectively, granted orphan drug designation to tominersen. Additionally in August 2018, the EMA granted PRIME designation to tominersen.

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.

Our Cardiovascular Medicines in Development

Our cardiovascular franchise includes investigational medicines that target the major risk factors of CVD.

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

Olezarsen – See the medicine description under "Our Phase 3 Pipeline" section above.

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

Fesomersen (FXI) – 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 for the treatment of a number of non-acute forms of thrombosis where additional safe and well tolerated anti-thrombotic medicines are needed.

In November 2022, Bayer presented positive results from the RE-THINc Phase 2b study of fesomersen in patients with end-stage renal disease, or ESRD, on hemodialysis at the ASN Kidney Week. In the study, fesomersen achieved its primary endpoint, demonstrating no increase in the incidence of the composite of major bleeding and clinically relevant non-major bleeding with 24 weeks of treatment. Fesomersen also achieved dose-dependent and sustained median reductions in steady-state FXI levels of 53.1%, 72.2% and 86.6% in the 40 mg, 80 mg, and 120 mg doses of fesomersen, respectively, administered once every four weeks. Incidences of dialysis circuit clotting and arteriovenous access, or AV-access, thrombosis diminished significantly with decreasing FXI levels, both of which were exploratory efficacy endpoints. Fesomersen had a favorable safety and tolerability profile supportive of continued development.

In November 2022, we regained all rights to fesomersen, which we had previously licensed to Bayer in February 2017.

ION904 (AGT) – ION904 is an investigational next-generation LICA medicine designed to inhibit the production of angiotensinogen to decrease blood pressure in people with uncontrolled hypertension. ION904 is a follow-on medicine targeting AGT, designed to enable less frequent dosing compared to IONIS-AGT-L_{Rx}.

In November 2023 at the AHA annual meeting we presented positive results from the Phase 2 clinical study of ION904 in patients with mild to moderate uncontrolled hypertension on one or more anti-hypertensive medications for at least one month. ION904 significantly reduced AGT levels compared to placebo. ION904 had a favorable safety and tolerability profile supportive of continued development.

Other Medicines for High Patient Need in Development

We also have other medicines for high patient need in development that are outside of our cardiovascular and neurological franchises that we believe could represent compelling opportunities for us, including our Specialty Rare medicines, donidalorsen and sapablursen.

1 Granted Otsuka exclusive rights to commercialize donidalorsen in Europe.

Donidalorsen – See the medicine description under "Our Phase 3 Pipeline" section above.

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 deficiency, such as polycythemia vera, or PV.

PV is a rare disease driven by a mutation in the *JAK2* gene that is potentially fatal and characterized 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 and symptoms such as fatigue and impaired cognitive function. There are no approved disease-modifying treatments for PV.

In January 2022, we initiated a Phase 2 study evaluating sapablursen in patients with phlebotomy dependent PV, 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 the 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. Sapablursen had a favorable safety and tolerability profile supportive of continued development.

In September 2020, the FDA granted Fast Track designation to sapablursen for polycythemia vera.

Bepirovirsen – See the medicine description under "Our Phase 3 Pipeline" section above.

IONIS-FB-L$_{Rx}$ (IgAN) – See the medicine description under "Our Phase 3 Pipeline" section above.

ION224 (DGAT2) – ION224 is an investigational LICA medicine we designed to reduce the production of diacylglycerol acyltransferase 2, or DGAT2, 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 CVD, 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.

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% of the global population has NAFLD, 1.5% to 6.5% have NASH, and up to 10% of NASH patients progress to advanced liver disease. There are currently no commercially available medications to treat NASH.

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.

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 in approximately 160 patients designed to assess the efficacy, safety and tolerability of multiple subcutaneous doses of ION224 on NASH histologic improvement.

IONIS-FB-L_{Rx} – IONIS-FB-L_{Rx} (RG6299) is an investigational LICA medicine we designed to inhibit the production of FB, and the alternative complement pathway. Genetic association studies have shown that overaction of the alternative complement pathway has been associated with the development of several complement-mediated diseases, including IgAN (see section above "Our Phase 3 Pipeline" for discussion of IgAN) and GA secondary to AMD.

AMD is the leading cause of central vision loss in developed countries. GA is an advanced form of AMD.

In June 2019, we initiated a Phase 2 GOLDEN study evaluating IONIS-FB-L_{Rx} in patients with GA secondary to AMD. The study is a randomized, masked, placebo-controlled study in approximately 330 patients 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. In August 2023, we announced that the GOLDEN study had completed enrollment.

In July 2022, Roche exercised its option to license IONIS-FB-L_{Rx} following the positive Phase 2 results for IgAN. As a result, Roche is responsible for global development, regulatory and commercialization activities, and costs for IONIS-FB-L_{Rx}, except for the open label Phase 2 study in patients with IgAN and the Phase 2 study in patients with GA, both of which we are conducting and funding.

ION839 (PNPLA3) – ION839 (AZD2693) is an investigational LICA medicine we designed to inhibit the production of patatin-like phospholipase domain-containing 3, or PNPLA3, protein. PNPLA3 is a protein that is found on the surface of intracellular lipid droplets. Studies have shown that a common genetic mutation of PNPLA3 is strongly associated with an increased risk for NASH. The mutant PNPLA3 protein is resistant to degradation, causing it to accumulate on the surface of lipid droplets, which disrupts the normal process for degrading lipid droplets, leading to increased liver fat accumulation, the underlying pathology of NASH.

In March 2023, AstraZeneca initiated a Phase 2b study of ION839 in patients with confirmed NASH with fibrosis and who are carriers of the PNPLA3 mutation. The Phase 2b study is a multi-center, randomized, double-blind, placebo-controlled clinical study in approximately 180 patients designed to assess the efficacy, safety and tolerability of multiple subcutaneous doses of ION839. The primary endpoint is the proportion of patients achieving NASH resolution without worsening of fibrosis based on histology after 52 weeks of treatment.

In April 2018, AstraZeneca exercised its option to license ION839. As a result, AstraZeneca is responsible for global development, regulatory and commercialization activities, and costs for ION839.

Our Technology

For three decades through our innovations in science and technology, we have enhanced the profiles of RNA-targeted medicines and pursued new opportunities in emerging areas of genetic medicine. Our recent technology advancements have enabled us to advance programs with the potential for extended dosing and delivery to new tissues, such as muscle. We have also added capabilities to utilize RNA interference, or RNAi, and potentially gene editing in addition to our novel antisense technology, which gives us the potential to deliver medicines to a greater number of people living with serious diseases.

Overview of Ionis' Technology

All of the medicines currently in our clinical pipeline use our antisense technology — 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. Most of our antisense medicines are designed to bind to mRNAs and inhibit the production of disease-causing proteins. Examples of these include WAINUA, olezarsen and donidalorsen. SPINRAZA is an example of an antisense medicine that modulates RNA splicing to increase protein production of the SMN protein, 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. Our antisense technology is also broadly applicable to many additional antisense mechanisms including decreasing toxic RNAs.

We also now use small interfering RNA (siRNA) technology, in addition to antisense technology, in the development of new medicines. Like antisense, siRNA medicines target RNA, and can decrease the production of specific proteins involved in disease. For each program we work on, we choose the approach which demonstrates the best potential product profile for the indication we are pursuing.

Our advanced LICA technology is a chemical technology we developed that involves attaching a molecule called a ligand that binds with receptors on the surface 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. We currently 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. Our LICA medicines have also demonstrated consistently favorable safety and tolerability in clinical trials, including in our Phase 3 studies of WAINUA (for ATTRv-PN), olezarsen (for FCS patients) and donidalorsen (for HAE).

Emerging Technology Advancements

Our recent technology advancements have enabled us to create even more potent medicines amenable to more potential targets and tissue types. We have also diversified the approaches we can use in designing our medicines in order to reach more patients with severe diseases. Today our medicines and those entering our pipeline utilize our key technology advances, including our Bicycle LICA technology, siRNA technology and MsPA backbone chemistry. And through our Metagenomi collaboration, we added the potential to use gene editing, which modifies DNA.

Mesyl phosphoramidate Backbone Chemistry

We designed our MsPA backbone chemistry to improve both therapeutic index and durability. It does this by increasing metabolic stability relative to the other backbone chemistries we utilize. We have also shown it can improve potency in certain circumstances and reduce non-specific interactions with proteins that can cause undesirable effects, such as proinflammatory effects. We currently have multiple new programs using our MsPA backbone, designed to improve both efficacy and durability, in preclinical development.

Bicycle Collaboration

In 2021, we entered into a collaboration with Bicycle Therapeutics that we expect can expand our LICA platform to target both skeletal and cardiac muscle, and potentially deliver medicines across the blood brain barrier. Bicycles are small, bicyclic peptides that have high affinity and selectivity for protein targets. Our collaboration with Bicycle allows us to utilize Bicycles that bind transferrin receptor 1 to facilitate the tissue specific delivery of oligonucleotide drugs (both antisense and siRNAs). We advanced our first Bicycle LICA program into preclinical development in 2023.

Gene Editing and Metagenomi Collaboration

In 2022, we entered into a collaboration with Metagenomi that leverages our extensive expertise in RNA-targeted therapeutics and Metagenomi's versatile next-generation gene editing systems to pursue a mix of validated and novel genetic targets with the goal of discovering and developing new drugs. These targets have the potential to expand therapeutic options for patients.

Gene editing utilizes specific RNA-guided nucleases known as Cas enzymes to precisely and permanently modify a DNA sequence. Because of this, gene editing holds the promise of treatments that could provide long-term, potentially permanent, therapeutic benefits.

Gene editing is highly complementary and synergistic with RNA-targeted therapeutics. Both platforms rely on the same nucleic acid hybridization principals to precisely target nucleases to either RNA, in the case of RNase H and siRNA drugs, or to DNA in the case of Clustered Regularly Interspaced Short Palindromic Repeats, or CRISPR-Cas systems. This enables us to leverage our expertise in nucleic acids and modified nucleic acid chemistry with the goal to enhance gene editing's ability to treat diseases for which there are limited treatment options.

Collaborative Arrangements

We have established alliances with a cadre of leading global pharmaceutical companies. Our partners include the following companies, among others: AstraZeneca, Biogen, GSK, Novartis, Otsuka 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 addition, we are eligible to receive royalties under our partnerships. Below, we include the significant terms of our collaboration agreements. For additional details, including other financial information, refer to Part IV, Item 15, Note 4, *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. In April 2023, the FDA granted accelerated approval for QALSODY (tofersen) in the U.S. to treat patients with SOD1-ALS. Biogen developed QALSODY under our 2013 strategic neurology collaboration. In addition, we and Biogen are currently developing numerous other investigational medicines to treat neurodegenerative diseases, including medicines in development to treat people with ALS, SMA, AS, AD, and PD. From inception through December 31, 2023, we have generated more than $3.8 billion in payments from our Biogen collaborations.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. 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. Under our agreement, Biogen is responsible for global development, regulatory and commercialization activities and costs for SPINRAZA. From inception through December 31, 2023, we recognized more than $2.0 billion in total revenue under our SPINRAZA collaboration, including more than $1.6 billion in revenue from SPINRAZA royalties and more than $425 million in R&D revenue.

New antisense medicines for the treatment of SMA

In 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.

In 2021, 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, including ION306, advance towards marketing approval.

Over the term of this collaboration, we are eligible to receive development, regulatory and sales milestone payments. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration. From inception through December 31, 2023, we have generated $85 million in payments under this collaboration.

Neurology Collaborations

2018 Strategic Neurology

In 2018, we and Biogen entered into a strategic collaboration to develop novel antisense medicines for a broad range of neurological diseases. We also entered into a Stock Purchase Agreement, or SPA. As a result, we received a payment related to the SPA in addition to an upfront payment at the commencement of this collaboration. 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. In most cases, Biogen will be responsible for conducting IND-enabling toxicology studies for the selected medicine. Biogen has 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.

For each medicine under this collaboration, we are eligible to receive a license fee, development milestone payments and regulatory milestone payments. 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 multiple programs under this collaboration. From inception through December 31, 2023, we have generated nearly $1.1 billion in payments under this collaboration.

2013 Strategic Neurology

In 2013, we and Biogen entered into a 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. In most cases, we are 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 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 four investigational medicines in development under this collaboration, including a medicine for Parkinson's disease (ION859), two medicines for ALS (QALSODY and ION541) and a medicine for multiple system atrophy (ION464). In 2018, Biogen exercised its option to license QALSODY, our medicine that received accelerated approval in April 2023 from the FDA for the treatment of adult patients with SOD1-ALS. As a result, Biogen is responsible for global development, regulatory and commercialization activities and costs for QALSODY.

Under the terms of the agreement, we 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.

Over the term of the collaboration for QALSODY, we are eligible to receive a license fee, development milestone payments and regulatory milestone payments. In addition, we are eligible to receive tiered royalties ranging from 11 percent to 15 percent on net sales of QALSODY.

For each of the other antisense molecules that are chosen for drug discovery and development under this collaboration, we are eligible to receive a license fee, development milestone payments and regulatory 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. From inception through December 31, 2023, we have generated more than $325 million in payments under our 2013 strategic neurology collaboration.

2012 Neurology

In 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, Biogen is conducting the IONIS-MAPT$_{Rx}$ study for AD and we are currently advancing 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 2019, Biogen exercised its option to license IONIS-MAPT$_{Rx}$ and as a result Biogen is responsible for global development, regulatory and commercialization activities and costs for IONIS-MAPT$_{Rx}$.

For each program under this collaboration, we are eligible to receive a license fee, development milestone payments and regulatory milestone payments, plus a mark-up on the costs 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. From inception through December 31, 2023, we have generated more than $230 million in payments under this collaboration.

Joint Development and Commercialization Arrangement

AstraZeneca

WAINUA (Eplontersen) Collaboration

In 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. In December 2023, the FDA approved eplontersen with the brand name, WAINUA, in the U.S. for ATTRv-PN. We are jointly developing and commercializing WAINUA with AstraZeneca in the U.S. We initially granted AstraZeneca exclusive rights to commercialize WAINUA outside the U.S., except for certain Latin American countries. In July 2023, we expanded those rights to include Latin America.

The collaboration includes territory-specific development, commercial and medical affairs cost-sharing provisions. AstraZeneca is currently responsible for 55 percent of the costs associated with the ongoing global Phase 3 development program. AstraZeneca is responsible for the majority of the commercial and medical affairs costs in the U.S. and all costs associated with bringing WAINUA to market outside the U.S.

Over the term of the collaboration, we are eligible to receive an upfront payment, license fee, development and approval milestone payments and sales milestone payments. In addition, we are eligible to receive up to mid-20 percent royalties for sales in the U.S. and tiered royalties ranging from mid to high teens for sales outside the U.S. From inception through December 31, 2023, we have generated more than $425 million in payments under this collaboration, including a milestone payment for the approval of WAINUA in the U.S. and revenue we earned from cost sharing provisions.

Research and Development Partners

AstraZeneca

In addition to our collaboration for WAINUA, we have a collaboration with AstraZeneca focused on discovering and developing treatments for cardiovascular, renal and metabolic diseases, which we formed in 2015. Under our collaboration, AstraZeneca has licensed multiple 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.

Over the term of the collaboration, we are eligible to receive an upfront payment, license fees, development milestone payments and regulatory milestone payments. 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 31, 2023, we have generated more than $340 million in payments under this collaboration.

GSK

In 2010, we entered into a collaboration with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for serious and rare diseases, including infectious diseases. Under our collaboration, GSK is developing bepirovirsen for the treatment of chronic 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.

Over the term of the collaboration, we are eligible to receive an upfront payment, a license fee, development milestone payments, regulatory milestone payments and sales milestone payments if GSK successfully develops and commercializes bepirovirsen. In addition, we are eligible to receive tiered royalties up to the low-teens on net sales of bepirovirsen. From inception through December 31, 2023, we have generated more than $105 million in payments under the HBV program collaboration.

Novartis

Pelacarsen Collaboration

In 2017, we initiated a collaboration with Novartis to develop and commercialize pelacarsen. Novartis is responsible for conducting and funding development and regulatory activities for pelacarsen, including a global Phase 3 cardiovascular outcomes study that Novartis initiated in 2019.

Over the term of the collaboration, we are eligible to receive an upfront payment, a license fee, a development milestone payment, regulatory milestone payments and sales milestone payments. We are also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of pelacarsen. From inception through December 31, 2023, we have generated more than $275 million in payments under this collaboration.

New Medicine for the Treatment of Lp(a)-Driven Cardiovascular Disease

In August 2023, we entered into a collaboration and license agreement with Novartis for the discovery, development and commercialization of a novel medicine for patients with Lp(a)-driven cardiovascular disease, or CVD. Novartis is solely responsible for the development, manufacturing and potential commercialization of the next generation Lp(a) therapy.

Over the term of the collaboration, we are eligible to receive an upfront payment, development milestone payments, regulatory milestone payments and sales milestone payments. In addition, we are eligible to receive tiered royalties ranging from 10 percent to 20 percent on net sales. From inception through December 31, 2023, we have generated $60 million in payments under this collaboration.

Roche

Huntington's Disease

In 2013, we entered into an agreement with Hoffmann-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 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen. As a result, Roche is responsible for all global development, regulatory and commercialization activities and costs for tominersen.

Over the term of the collaboration, we are eligible to receive a license fee, development milestone payments, regulatory milestone payments and sales milestone payments as tominersen advances. In addition, we are eligible to receive 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 collaboration. From inception through December 31, 2023, we have generated more than $150 million in payments under this collaboration.

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

In 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 IgAN and one for the treatment of patients with GA, the advanced stage of dry AMD. In April 2023, Roche initiated a Phase 3 study of IONIS-FB-L_{Rx} in patients with IgAN.

After positive data from a Phase 2 clinical study in patients with IgAN, Roche licensed IONIS-FB-L_{Rx} in 2022. As a result, Roche is responsible for global development, regulatory and commercialization activities, and costs for IONIS-FB-L_{Rx}, except for the open label Phase 2 study in patients with IgAN and the Phase 2 study in patients with GA, both of which we are conducting and funding.

Over the term of the collaboration, we are eligible to receive an upfront payment, a license fee, development milestone payments, regulatory milestone payments and sales milestone payments. In addition, we are also eligible to receive tiered royalties from the high teens to 20 percent on net sales. From inception through December 31, 2023, we have generated more than $135 million in payments under this collaboration.

RNA-Targeting Medicines for Alzheimer's Disease and Huntington's Disease

In September 2023, we entered into an agreement with Roche to develop two undisclosed early-stage programs for RNA-targeting investigational medicines for the treatment of AD and HD. Under the agreement, we are responsible for advancing the two programs through preclinical studies and Roche is responsible for clinical development, manufacturing and commercialization of the medicines if they receive regulatory approval.

Over the term of the collaboration, we are eligible to receive an upfront payment, development milestone payments and sales milestone payments. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales. From inception through December 31, 2023, we have generated $60 million in payments under this collaboration.

Commercialization Partnerships

Otsuka

In December 2023, we entered into an agreement with Otsuka Pharmaceutical Co., Ltd., or Otsuka, to commercialize donidalorsen in Europe. We are responsible for the ongoing development of donidalorsen. We retained the rights to commercialize donidalorsen in the U.S. and in the rest of the world assuming regulatory approval.

Over the term of the collaboration, we are eligible to receive an upfront payment, regulatory milestone payments and sales milestone payments. In addition, we are eligible to receive tiered royalties ranging from 20 percent to 30 percent on net sales of donidalorsen in Europe. From inception through December 31, 2023, we have generated $65 million in payments under this collaboration.

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 and September 2023, we started receiving royalties from PTC for TEGSEDI and WAYLIVRA sales, respectively.

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. Refer to the section titled, *Overview*, for further details on our distribution agreement with Sobi.

Technology Enhancement Collaborations

Bicycle Therapeutics

In 2020, we entered into a collaboration agreement with Bicycle Therapeutics, or Bicycle, and obtained an option to license its peptide technology to potentially increase the delivery capabilities of our LICA medicines. In 2021, we exercised our option to license Bicycle's technology. Our payment to Bicycle for licensing its technology included an equity investment in Bicycle.

Metagenomi

In 2022, we entered into a collaboration and license agreement with Metagenomi to research, develop and commercialize investigational medicines for up to four initial genetic targets, and, upon the achievement of certain development milestones, four additional genetic targets using gene editing technologies. As a result, we paid Metagenomi to license its technologies and will pay Metagenomi certain fees for the selection of genetic targets. In addition, we will pay Metagenomi milestone payments and royalties that are contingent on the achievement of certain development, regulatory and sales events. We will also reimburse Metagenomi for certain of its costs in conducting its research and drug discovery activities under the collaboration.

Vect-Horus

In December 2023, we entered into a license agreement with Vect-Horus to provide us with worldwide, exclusive license for a specified number of targets using Vect-Horus' platform technology "VECTrans" for systemic delivery of RNA-targeted therapeutics that can cross the blood-brain barrier and address targets in the central nervous system. As a result, we paid Vect-Horus to license its technologies. In addition, we will pay Vect-Horus milestone payments and royalties that are contingent on the achievement of certain development, regulatory and sales events.

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.

Manufacturing

We manufacture most of the active pharmaceutical ingredient, or API, we use for our research and development, or R&D, 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 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 material and/or commercial drug supply for our partners. For example, in the past we have manufactured clinical trial material for AstraZeneca, Biogen, GSK and Novartis and commercial drug supply 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. We and/or our CMOs 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 CMOs 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 CMOs.

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

Specifically, we have the following in place for our commercial medicines and our medicines in Phase 3 development.

SPINRAZA

Biogen is responsible for SPINRAZA drug supply.

QALSODY

Biogen is responsible for QALSODY drug supply.

WAINUA

AstraZeneca is responsible for WAINUA's commercial drug supply. Our CMOs supplied the API and the finished drug product for WAINUA's Phase 3 program. Pursuant to our collaboration with AstraZeneca, we will manufacture and supply WAINUA using CMOs for the ongoing clinical trials, process performance qualification batches and pre-approval inspection batches.

TEGSEDI and WAYLIVRA

For TEGSEDI's commercial drug supply, we are using CMOs to produce API and finished goods. For WAYLIVRA's commercial drug supply, we are using API that we have manufactured and CMOs to produce the finished goods.

Olezarsen, Donidalorsen, Zilganersen, Ulefnersen

We and/or our CMOs have supplied the API and the finished drug product for olezarsen, donidalorsen, zilganersen and ulefnersen that we believe will be sufficient through the completion of the Phase 3 programs for each medicine, including process performance qualification batches and pre-approval inspection batches. We plan to leverage our relationships with CMOs to maintain long-term supply at competitive prices in the future.

Pelacarsen

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

Bepirovirsen

We supplied API for bepirovirsen's Phase 1 and Phase 2 programs. Pursuant to our collaboration with GSK, GSK is responsible for any further bepirovirsen drug supply.

IONIS-FB-L_{Rx}

We supplied API for the IONIS-FB-L_{Rx} Phase 1 and Phase 2 IgAN programs. Pursuant to our collaboration with Roche, Roche is responsible for any further drug supply for the IONIS-FB-L_{Rx} program.

Commercial Operations

We have established sales and marketing capabilities to support our commercial launch of WAINUA in the U.S. and anticipated near-term commercial launches of olezarsen and donidalorsen. We began with our co-commercialization partnership with AstraZeneca for WAINUA in which we combine our experience in RNA-targeted therapeutics and deep knowledge of the TTR amyloidosis market with AstraZeneca's global scale in drug development and commercialization to enable market penetration for the benefit of patients.

As we approach our first potential independent commercial launches of olezarsen and donidalorsen in the U.S., we have been refining our portfolio strategy and recruiting experienced professionals with relevant backgrounds in sales, marketing, patient education, market access, portfolio planning and market insight, new product commercial strategy and commercial operations in the pharmaceutical industry. We are focused on developing a unique and innovative approach to bring our medicines to patients living with serious diseases. We have built core capabilities and a commercial platform with the ability to scale as needed to meet our current and future commercialization needs. We plan to build our field sales teams as we approach each of our launches.

In addition, we recently entered into a European licensing agreement with Otsuka for donidalorsen in HAE in which we will leverage Otsuka's strong commercial infrastructure and rare disease experience to reach European HAE patients.

Medical Affairs

We have built medical affairs capabilities to disseminate information about our medicines and increase disease awareness through various channels of communication with key stakeholders. Our medical affairs function is responsible for funding and coordinating investigator-sponsored trials, communicating scientific and clinical information to healthcare providers, medical professionals and patients, and managing publications.

Intellectual Proprietary Rights

We rely on patents, trademarks, trade secrets, and proprietary know-how to develop and maintain a competitive position in RNA-targeted therapeutics generally and to protect our investment in specific products. To this end, we focus our resources on intellectual property, or IP, that drives value for our company.

Product-Specific IP

Each of our medicines is protected worldwide by product-specific patents claiming oligonucleotides having the nucleobase sequences and chemical modifications of our medicines; and methods of achieving cellular or clinical endpoints using such oligonucleotides. We pursue such patents 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 regulatory review. Expiration dates listed below do not reflect any such extensions.

Commercial products are also protected by trademarks filed throughout the world.

Marketed Products

SPINRAZA and Survival Motor Neuron 2

Patents

We believe SPINRAZA (nusinersen) 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, (ii) joint patents with Cold Spring Harbor Laboratory claiming fully modified 2'-MOE compounds targeting SMN2, including the precise composition of matter of SPINRAZA and methods of using such compositions; and (iii) dosing and therapeutic methods of using such compounds and compositions. 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

Trademarks

The name "SPINRAZA" is protected throughout the world by trademarks owned by our commercial partner Biogen. Particulars for the United States and European marks are listed below:

Jurisdiction	Registration No.	Mark	
United States	5156572	SPINRAZA	(word mark)
Europe	013388145	SPINRAZA	(word mark)
Europe	014812291 and 015309941	SPINRAZA	(design mark)

QALSODY and SOD-1

Patents

We believe QALSODY is protected from generic competition in the U.S. and Europe until at least 2035. Additional patent applications designed to protect QALSODY in other foreign jurisdictions are being pursued. With Biogen's license of QALSODY, we assigned our interest in these patents to Biogen. The table below lists some key issued patents protecting QALSODY 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 QALSODY
United States	10,669,546	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Methods of treating a SOD-1 associated neurodegenerative disorder by administering QALSODY
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 QALSODY
Europe	3126499	COMPOSITIONS FOR MODULATING SOD-1 EXPRESSION	2035	Composition of QALSODY

Trademarks

The name "QALSODY" is protected throughout the world by trademarks owned by our commercial partner Biogen. Particulars for the United States and European marks are listed below:

Jurisdiction	Registration No.	Mark	
United States	7164425	QALSODY	(word mark)
United States	7116182	QALSODY	(design mark)
Europe	1542485	QALSODY	(word mark)
Europe	018517819	QALSODY	(design mark)

WAINUA and Transthyretin

Patents

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

Trademarks

The name "WAINUA" is protected by trademarks owned by our commercial partner Astra Zeneca. Particulars for the United States marks are listed below:

Jurisdiction	Application No.	Mark	
United States	98054331	WAINUA	(word mark)
United States	98228658		(design mark)

TEGSEDI and Transthyretin

Patents

We believe TEGSEDI (inotersen) is protected from generic competition in the U.S. and Europe until at least 2031. 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

Trademarks

The name "TEGSEDI" is protected by trademark throughout the world. Particulars for the United States and European marks are listed below:

Jurisdiction	Registration No.	Mark	
United States	5740635	TEGSEDI	(word mark)
Europe	017224742	TEGSEDI	(word mark)

WAYLIVRA and Apolipoprotein C-III

Patents

We believe WAYLIVRA (volanesorsen) is protected from generic competition in Europe until at least 2034. 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. The table below lists some key issued patents protecting WAYLIVRA in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
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 that hybridize within the nucleotide region of apo-CIII targeted by WAYLIVRA
Europe	3002007	MODULATION OF APOLIPOPROTEIN C-III EXPRESSION	2024	Antisense compounds complementary to an apo-CIII nucleic acid for use in therapy
United States	9,157,082	MODULATION OF APOLIPOPROTEIN C-III (APOCIII) EXPRESSION	2032	Methods of using apo-CIII antisense compounds 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 apo-CIII specific inhibitor wherein triglyceride levels are reduced
Europe	2956176	MODULATION OF APOLIPOPROTEIN C-III (APOCIII) EXPRESSION IN LIPOPROTEIN LIPASE DEFICIENT (LPLD) POPULATIONS	2034	Apo-CIII specific inhibitors including WAYLIVRA for treating lipoprotein lipase deficiency or FCS

Trademark

The name “WAYLIVRA” is protected by trademark in Europe. Particulars for the European mark are listed below:

Jurisdiction	Registration No.	Mark
Europe	016409609	WAYLIVRA (word mark)

Phase 3 Programs

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

Zilganersen and GFAP

We believe zilganersen is protected from generic competition in the U.S. until at least 2041. A patent application designed to protect zilganersen from generic competition is being pursued in Europe; a patent issuing from that application would have term until at least 2041. The table below lists a key issued patent protecting zilganersen in the U.S. and a pending application in Europe:

Jurisdiction	Patent No. (Patent Application No.)	Title	Expiration	Description of Claims
United States	11,786,546	COMPOUNDS AND METHODS FOR MODULATING GFAP	2041	Composition of zilganersen
Europe	(20846055.0)	COMPOUNDS AND METHODS FOR MODULATING GFAP	2041	Composition of zilganersen

Ulefnersen and FUS

Patent applications designed to protect ulefnersen from generic competition are being pursued in the U.S. and Europe. Patents issued from these applications would have terms until at least 2040. The table below lists some key pending patent applications designed to protect ulefnersen in the U.S. and Europe:

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

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 are 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

Bepirovirsen and Hepatitis B Virus

We believe bepirovirsen is protected from generic competition in the U.S. and Europe until at least 2032. Additional patent protection designed to protect bepirovirsen in other foreign jurisdictions are being pursued. With GSK's license of bepirovirsen, we assigned our interest in these patents to GSK. The table below lists some key issued patents protecting bepirovirsen in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	8,642,752	MODULATION OF HEPATITIS B VIRUS (HBV) EXPRESSION	2032	Composition of bepirovirsen
Europe	3505528	MODULATION OF HEPATITIS B VIRUS (HBV) EXPRESSION	2032	Composition of bepirovirsen

IONIS-FB-L_{Rx} and Factor B

We believe IONIS-FB-L_{Rx} is protected from generic competition in the U.S. and Europe until at least 2035. Additional patent protection designed to protect IONIS-FB-L_{Rx} in other foreign jurisdictions are being pursued. The table below lists some key issued patents protecting IONIS-FB-L_{Rx} in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
Europe	3043827	MODULATORS OF COMPLEMENT FACTOR B	2034	Compound comprising the antisense oligonucleotide portion of IONIS-FB-L_{Rx}.
United States	10,280,423	COMPOSITIONS AND METHODS FOR MODULATING COMPLEMENT FACTOR B EXPRESSION	2035	Composition of IONIS-FB-L_{Rx}.
Europe	3137596	COMPOSITIONS AND METHODS FOR MODULATING COMPLEMENT FACTOR B EXPRESSION	2035	Composition of IONIS-FB-L_{Rx}.

Platform IP

In addition to the IP that provides exclusivity for specific products, we also pursue IP that provides exclusivity for our core technology in the field of oligonucleotides and RNA-targeting therapeutics more generally. Our core technology patents include claims to chemically modified oligonucleotides as well as designs utilizing these chemical modifications. Because these core claims are independent of specific therapeutic target, nucleic acid sequence, or clinical indication, they may reach several products.

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 medicines to increase their therapeutic efficacy. The following are some of our patents in this category in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
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
United States	7,569,686	COMPOUNDS AND METHODS FOR SYNTHESIS OF BICYCLIC NUCLEIC ACID ANALOGS	2027	Methods of synthesizing cEt 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
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
United States	11,629,348	LINKAGE MODIFIED OLIGONUCLEOTIDES AND USES THEREOF	2040	Gapmer oligonucleotides having 2-4 mesyl phosphoramidate internucleoside linkages at specified positions in the gap

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 No.	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

Manufacturing

We also own patents claiming methods of manufacturing and purifying oligonucleotides and related compounds. These patents claim methods for improving oligonucleotide drug manufacturing, including processes for large-scale oligonucleotide synthesis and purification.

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. 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.

Pricing and Reimbursement

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 that 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 U.S. FDA-approved products for a particular indication. Moreover, a payer's decision to provide coverage for a medicine does not imply that an adequate reimbursement rate will be approved. Additionally, coverage and reimbursement for drugs can differ significantly from payer to payer. One third-party payer's decision to cover a particular medicine does not ensure that other payers will also provide coverage for the medicine or will provide coverage at an adequate reimbursement rate.

Third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medicines and services, in addition to their safety and efficacy. To obtain coverage and reimbursement for any medicine that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies to demonstrate the medical necessity and cost-effectiveness of our medicine. These studies will be in addition to the studies required to obtain regulatory approvals. If third-party payers do not consider a medicine to be cost-effective compared to other available therapies, they may not cover the medicine after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to sell such medicine at a profit.

In certain jurisdictions, governments may also regulate or influence coverage, reimbursement and/or pricing of our medicines to control cost or affect use. In the European community, governments influence the price of drugs through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those medicines to consumers. Some jurisdictions operate positive and negative list systems under which medicines may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical studies that compare the cost effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines but monitor and control company profits.

The marketability of any medicine for which we receive regulatory approval for commercial sale may suffer if the government and third-party payers fail to provide adequate coverage and reimbursement. In addition, the focus on cost containment measures in the U.S. and other countries has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if we attain favorable coverage and reimbursement status for one or more medicines for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Healthcare Reform

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 report that outlined principles for drug pricing reform and set out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS could take to advance these principles. Congress is also considering additional health reform measures that may result in decreased reimbursement, which may further exacerbate industry-wide pressure to reduce the prices charged for medical products.

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. For example, in August 2022, President Biden signed the Inflation Reduction Act of 2022, or the IRA, into law, which includes key actions aimed at reducing the costs of prescription drugs and allows HHS to negotiate the price of certain single-source drugs covered under Medicare and establish a price cap on such drugs, known as the Maximum Fair Price. There are important exemptions to the Maximum Fair Price, including for medications that are orphan drug designated and approved for only one rare disease, and drugs with low Medicare spend as defined by the Centers for Medicare & Medicaid Services. Specifically, in an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation under the IRA requires, among other things, (1) a cap on out-of-pocket drug spending under Part D, (2) drug manufacturers to pay a rebate to the federal government if prices for drugs covered under Part D and Part B increase faster than the rate of inflation, and (3) drug manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions take effect progressively starting in fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges. In response to the Biden administration's October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs using march-in rights under the Bayh-Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march-in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework.

Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. Our future product sales may be subject to additional discounts from list price in the form of rebates and discounts provided to 340B covered entities. Changes to the 340B program or to Medicare or Medicaid programs at the federal or state level, including outcomes of ongoing litigation in our industry, may impact our product prices and rebate liability.

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 sets 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 HHS 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 HHS, 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 tested and the FDA approved. 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, healthcare reform legislation has strengthened these laws. For example, the Patient Protection and Affordable Care 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. Further, HIPAA also 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. 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, corporate integrity agreements, and could include criminal penalties. 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. As described above, other healthcare laws that may affect our ability to operate include HIPAA, 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. 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.

As discussed above, 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, including new models aimed to lower of cost of drugs, promote accessibility, and improve quality of care and initiatives to control the price of prescription drugs using march-in rights under the Bayh-Dole Act.

The Foreign Corrupt Practices Act

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. In addition, 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 contract research organizations, contract manufacturing organizations, distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. Importantly, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions.

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 genetic medicines 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 commercial medicines and our medicines in 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 administration, marketing and sales strategy and tactics, availability, price, and reimbursement.

Below we have included what we believe to be medicines that compete or may compete directly with our marketed medicines and the medicines we currently have in Phase 3 trials. We included competitors, potential competitors that are past Phase 1 development or potential competitors that plan to start a pivotal study this year.

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 in pediatric and adult patients	Oral
OAV101 (Onasemnogene abeparvovec)	Novartis	Gene therapy targeting the genetic root cause of SMA by replacing the missing or nonworking SMN1 gene	Phase 3	Intrathecal injection

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

QALSODY

We believe that the following medicine could compete with QALSODY in SOD1-ALS:

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
NI-005 / AP-101	Neurimmune (AL-S Pharma) / Lilly	A human derived antibody targeting misfolded SOD1	Phase 2	Intravenous Infusion

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

WAINUA and TEGSEDI

We consider the following medicines as competitors and potential future competitors to WAINUA and TEGSEDI for ATTRv-PN and/or ATTR-CM:

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	Received CRL in the U.S. for ATTR-CM Approved in US, EU, Japan and select other markets for ATTRv-PN	Intravenous infusion
Vyndaqel/Vyndamax (Tafamidis and tafamidis meglumine)	Pfizer	A small molecule medicine to stabilize TTR protein	Approved in EU, Japan and select other markets for ATTRv-PN, ATTR-CM; indications vary by region	Oral
Amvuttra (Vutrisiran)	Alnylam	An RNAi medicine conjugated with GalNAc to inhibit TTR mRNA	Approved for ATTRv-PN in the U.S., EU and Japan, Phase 3 for ATTR-CM	Subcutaneous Injection
Acoramidis	BridgeBio	Small molecule that binds and stabilizes TTR in the blood	Submitted in U.S., EU and Japan	Oral
NTLA-2001	Intellia/ Regeneron	CRISPR therapeutic candidate designed to reduce circulating TTR protein levels	Phase 3 ATTR-CM	Intravenous Infusion
ALXN2220	AstraZeneca	A monoclonal IgG1 which acts by targeting and depleting TTR protein	Phase 3 ATTR-CM	Intravenous Infusion
NNC6019-0001	Novo Nordisk	A monoclonal antibody to deplete amyloid via antibody-mediated phagocytosis	Phase 2 ATTR-CM	Intravenous Infusion

(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 (Plozasiran)	Arrowhead	Targets APOCIII by utilizing Targeted RNAi Molecule Platform	Phase 3 FCS, Phase 2 SHTG	Subcutaneous Injection
Pegozafermin	89bio	FGF21 analog	Phase 3 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 two years and older	Subcutaneous Injection
Cinryze (C1 esterase inhibitor)	Takeda	A human plasma protein that mediates inflammation and coagulation	Approved for HAE patients six 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 Injection
Garadacimab	CSL Behring	An anti-factor XIIa monoclonal antibody	Under regulatory review in the U.S. and EU	Subcutaneous Injection
Deucrictibant	Pharvaris	An oral B2-receptor antagonist	Phase 2	Oral
STAR-0215	Astria	A monoclonal antibody inhibitor of plasma kallikrein	Phase 2	Subcutaneous Injection
NTLA-2002	Intellia	CRISPR therapeutic candidate designed to inactivate the kallikrein B1 gene	Phase 1/2	Intravenous Infusion

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

Zilganersen

We believe there are no medicines in clinical development for AxD.

Ulefnersen

We believe there are no medicines in clinical development for FUS-ALS.

Pelacarsen

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

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
Olpasiran	Amgen/ Arrowhead	RNAi therapeutic designed to lower Lp(a)	Phase 3	Subcutaneous Injection
Zerlasiran	Silence	RNAi therapeutic designed to lower Lp(a)	Phase 2	Subcutaneous Injection
Lepodisiran	Lilly	RNAi therapeutic designed to lower Lp(a)	Phase 2	Subcutaneous Injection
Muvalaplin	Lilly	Small molecule therapy to lower Lp(a)	Phase 2	Oral

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

Bepirovirsen

We believe that the following medicines could compete with bepirovirsen in HBV:

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
Elebsiran (VIR-2218)	Vir Biotech / Alnylam	RNAi therapeutic to reduce HBV viral antigens	Phase 2	Subcutaneous Injection
Imdusiran (AB-729)	Arbutus Biopharma	RNAi therapeutic to reduce HBV viral antigens	Phase 2	Subcutaneous Injection
Xalnesiran	Roche	RNAi therapeutic to reduce HBV viral antigens	Phase 2	Subcutaneous Injection

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

IONIS-FB-L$_{Rx}$

We believe that the following medicines could compete with IONIS-FB-L$_{Rx}$ in IgAN:

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
Tarpeyo (budesonide)	Calliditas	A corticosteroid indicated to reduce proteinuria in adults with primary IgAN	Approved for IgAN	Oral
Filspari (Sparsentan)	Travere	An endothelin & angiotensin II receptor antagonist to reduce proteinuria in adults with primary IgAN	Approved for IgAN	Oral
Atrasentan	Novartis (Chinook)	An endothelin A receptor antagonist	Phase 3 (IgAN)	Oral
Iptacopan	Novartis (Chinook)	A factor B inhibitor of the alternative complement pathway	Phase 3 (IgAN)	Oral
Zigakibart	Novartis (Chinook)	An anti-APRIL monoclonal antibody	Phase 3 (IgAN)	Subcutaneous Injection
Sibeprenlimab	Otsuka (Visterra)	A humanized IgG2 monoclonal antibody that inhibits APRIL	Phase 3 (IgAN)	Intravenous Infusion
Atacicept	Vera	A recombinant fusion protein a dual inhibitor of BLyS and APRIL	Phase 3 (IgAN)	Subcutaneous Injection
Ravulizumab	Alexion (AstraZeneca)	A humanized monoclonal antibody to complement factor 5	Phase 2 (IgAN)	Subcutaneous Injection
Vemircopan	Alexion (AstraZeneca)	A complement factor D inhibitor	Phase 2 (IgAN)	Oral
Felzartamab	Hi-Bio	A monoclonal antibody directed against CD38	Phase 2 (IgAN)	Intravenous Infusion

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

We believe that the following medicines could compete with IONIS-FB-L_{Rx} in GA:

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
Ivervay (avacincaptad pegol)	Iveric Bio	A complement C5 inhibitor approved for GA secondary to AMD	Approved (GA)	Intravitreal
Syfovre (pegcetacoplan)	Apellis	A complement C5 inhibitor approved for GA secondary to AMD	Approved (GA)	Intravitreal
Tinlarebant	Belite Bio	A small molecule RBP4 antagonist	Phase 3 (GA)	Oral
Danicopan	Alexion	A factor D inhibitor	Phase 2 (GA)	Oral
PPY988 (GT005)	Novartis	A gene therapy with encoding for human complement factor I	Phase 2 (GA)	Intraocular
AVD-104	Aviceda	A glycomimetic nanoparticle	Phase 2 (GA)	Intravitreal
ANX007	Annexon Bio	A fragment antigen-binding (fab) antibody	Phase 2 (GA)	Intravitreal

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

Corporate Responsibility and Environmental, Social and Governance Initiatives

We believe operating responsibly and sustainably creates long-term value for our company and our stakeholders. We recognize the importance of Corporate Responsibility, or CR, and Environmental, Social and Governance, or ESG, initiatives as it relates to our business strategy and risk assessment. In 2023, we continued to evolve our CR program by building on our foundation and further defining our strategic direction. This includes completing our first CR materiality assessment, updating our CR framework to better focus on our ESG priorities and developing goals to drive and measure our performance.

We began reporting on CR metrics in 2021 and have continued to expand disclosure since then. In 2023, we established three strategic CR pillars that we believe are most important to our business:

Ionis Corporate Responsibility Strategic Pillars

Innovate to improve the lives of people with serious diseases	Empowering our employees and communities	Operating responsibly and sustainably
We innovate across the business and work tirelessly to discover, develop and deliver important new medicines for people with serious diseases.	*We are committed to fostering an inclusive culture that drives excellence, embraces diversity, and supports our communities.*	*We operate with integrity to help create a better, more sustainable future for all through environmental stewardship and responsible business practices and stakeholder interactions.*
• Innovation and R&D • Access and Affordability • Patient Advocacy and Engagement	• Workplace Culture, Talent Attraction and Development • Diversity, Equity and Inclusion • Social Impact and Community Engagement	• Environmental Sustainability • Governance and Integrity • Data Privacy and Cybersecurity

Our CR initiatives are driven by our Chief Executive Officer and executive-level CR Steering Committee, or CR Committee. The CR Committee consists of senior leaders in key functions across the company, including legal, finance, investor relations, human resources, research and development, manufacturing, commercial, compliance and corporate affairs. In 2023, we expanded our CR Committee to include a broader cross-section of senior leaders to ensure we continue to develop the right programs and policies.

The CR Committee is part of our governance framework, which defines responsibilities and ensures we have the right systems and controls to oversee ethical and sustainable operations across our business. Our Board of Directors oversees our overall CR strategy and management of material ESG risks and opportunities and receives updates related to corporate governance and corporate responsibility from the CR Committee at least once annually. In 2023, the Nominating, Governance and Review Committee assumed responsibility for CR and ESG-related matters.

We look to our stakeholders and third-party frameworks such as the Sustainability Accounting Standards Board Health Care – Biotechnology and Pharmaceuticals Standard and the Task Force on Climate-Related Financial Disclosures to inform our approach and our disclosures.

We will share more details on our updated CR framework, goals and ESG initiatives in our 2023 CR Report, which will be published in April 2024 and available on our website. Nothing in the report or on our website shall be deemed incorporated by reference into this Annual Report on Form 10-K.

Employees and Human Capital

As of February 15, 2024, we employed 927 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 2023 was 7 percent, while the turnover for life sciences and medical device companies over this period was 23 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

We reward our employees 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 an 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;
- Family care benefits;
- Life, AD&D insurance and long-term disability insurance coverage options; and
- Employee Assistance Program, or EAP.

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

Pay Equity

We are committed to paying our employees fairly, regardless of their gender, ethnicity, race, age 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, in terms of our overall workforce and individual employees, to ensure our pay is fair and equitable.

On an annual basis, we monitor our pay equity status and market competitiveness, and perform a pay equity analysis that reviews pay equity by gender, ethnicity, race and age. Our 2023 pay equity analysis confirmed we do not have a statistically significant difference in pay for the same or similar work, regardless of gender, ethnicity, race or age.

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 at Ionis. 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 having a bias to act 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 15, 2024:

Name	Age	Position
Brett P. Monia, Ph.D.	62	Chief Executive Officer
Joseph T. Baroldi	46	Executive Vice President, Chief Business Officer
Brian Birchler	58	Executive Vice President, Corporate and Development Operations
C. Frank Bennett, Ph.D.	67	Executive Vice President, Chief Scientific Officer
Onaiza Cadoret-Manier	59	Executive Vice President, Chief Global Product Strategy and Operations Officer
Richard S. Geary, Ph.D.	66	Executive Vice President, Chief Development Officer
Elizabeth L. Hougen	62	Executive Vice President, Finance and Chief Financial Officer
Patrick R. O'Neil, Esq.	50	Chief Legal Officer, General Counsel and Corporate Secretary
Eugene Schneider, M.D.	51	Executive Vice President, Chief Clinical Development and Operations Officer
Eric E. Swayze, Ph.D.	58	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, M.A., M.B.A., M.S.

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, Business Development at Ionis, where he held several roles of increasing responsibility from 2009 to 2020. Mr. Baroldi has also held positions in strategic planning and scientific research for Gen-Probe Inc.

BRIAN BIRCHLER

Executive Vice President, Corporate and Development Operations

Mr. Birchler has served as Ionis' Executive Vice President, Corporate and Development Operations since March 2022. From January 2008 to March 2022, Mr. Birchler served as our Senior Vice President, Drug Development Operations. From January 2005 to January 2008 he served as our Vice President, Drug Development Operations and from January 2003 to January 2005, as our Vice President, Development Chemistry and Operations. Mr. Birchler joined Ionis in 1995 as Senior Scientist/Senior Research Associate. Prior to joining Ionis, Mr. Birchler was employed by CIBA Vision Corp. and Burroughs Wellcome Pharmaceuticals in various engineering, development and commercial positions.

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 Global 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 and Operations Officer

Dr. Schneider has served as Ionis' Executive Vice President and Chief Clinical Development and Operations Officer since September 2023. From January 2021 to September 2023, Dr. Schneider served as our Executive Vice President and Chief Clinical Development Officer. 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 Commercialization of our Medicines

We have limited experience as a company in commercializing medicines and we will have to continue to invest significant resources to develop our 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 currently rely on third parties for the commercialization of our marketed medicines, have limited experience as a company in commercializing medicines and will have to continue 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 continue 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 continue to 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 our commercial medicines 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, 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 our commercial medicines 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 in the past disclosed that SPINRAZA revenue 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 our commercial medicines 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 of the medicines that we or our partners may develop.

For example, TEGSEDI requires periodic blood and urine monitoring and is available in the U.S. only through a risk evaluation and mitigation strategy, or REMS program. In addition, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis. Our main external competitors in the U.S. market for TEGSEDI are patisiran and vutrisiran, both marketed by Alnylam Pharmaceuticals, Inc. Neither patisiran nor vutrisiran has a boxed warning nor does either require use of a REMS program. Additionally, the product label for WAYLIVRA in the European Union, or 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 government or other third-party payers fail to provide adequate coverage and payment rates for our medicines, including our commercial medicines 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, our commercial medicines and our medicines in development will face competition from other therapies and medicines for limited financial resources. Furthermore, 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. In addition, third-party payers may never consider our future products as cost-effective and 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, or ACA, 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 ACA, as well as efforts to repeal or replace certain aspects of the ACA. It is unclear how future litigation and healthcare reform measures will impact the ACA 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, increase competition (including by enhancing support for generic and biosimilar drugs), lower out-of-pocket drug costs for patients, curtail spread pricing practices by pharmacy benefit managers, and foster scientific innovation to promote better health care and improved health. In addition, the Inflation Reduction Act of 2022, or the IRA, includes key actions aimed at reducing the costs of prescription drugs and allows HHS to negotiate the price of certain single-source drugs covered under Medicare and establish a price cap on such drugs. Specifically, in an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation under the IRA requires, among other things, (1) a cap on out-of-pocket drug spending under Part D, (2) drug manufacturers to pay a rebate to the federal government if prices for drugs covered under Part D and Part B increase faster than the rate of inflation, and (3) drug manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions take effect progressively starting in fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges. In response to the Biden administration's October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs using march-in rights under the Bayh-Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march-in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework. It is unclear whether or how these selected models or similar policy initiatives will impact prescription drug pricing in the future.

Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. Our future product sales may be subject to additional discounts from list price in the form of rebates and discounts provided to covered entities under the Public Health Service Act 340B drug pricing program. Changes to the 340B program or to Medicare or Medicaid programs at the federal or state level, including outcomes of ongoing litigation in our industry, may impact our product prices and rebate liability.

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. For example, on January 5, 2024, the FDA approved Florida's Section 804 Importation Program, or SIP, proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs. Third-party coverage and reimbursement for medicines may not be available or adequate in either the U.S. or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

If we or our partners fail to compete effectively, our medicines, including our commercial medicines 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. In addition, other companies are engaged in developing RNA-targeted 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 our commercial medicines 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 some of 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 our commercial medicines and our medicines in development.

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 or more successfully commercialize their products.

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;
- Taldefgrobep alfa, Evrysdi + GYM329 and NMD670 could compete with SPINRAZA;
- Patisiran, tafamidis, tafamidis meglumine and vutrisiran compete with TEGSEDI and WAINUA;
- Acoramidis, NTLA-2001 and NNC6019-0001 could compete with TEGSEDI and WAINUA;
- ARO-APOC3 and pegozafermin could compete with WAYLIVRA and olezarsen;
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, deucrictibant, NTLA-2002 and STAR-0215 could compete with donidalorsen;
- Olpasiran, zerlasiran, lepodisiran and muvalaplin could compete with pelacarsen;
- NI-005/AP-101 could compete with QALSODY;
- VIR-2218 + PEG-IFN-α, VIR-3434 ± VIR-2218 ± PEG-IFN-α, VIR-2218 + BRII-179, NI-204VIR-2218 + GS-9688 + nivolumab, AB-729, imdusiran + Peg-IFNa-2α + NA, xalnesiran + RG6084 + NA, xalnesiran + NA, xalnesiran + pegIFN + NA, xalnesiran + RO7049389 + NA, xalnesiran + ruzotolimod + NA, RO7049389 + ruzotolimod + NA could complete with bepirovirsen; and
- Budesonide, sparsentan, atrasentan, iptacopan, zigakibart, sibeprenlimab, atacicept, ravulizumab, vemircopan, felzartamab, povetacicept, avacincaptad pegol, pegcetacoplan, tinlarebant, danicopan, GT005, AVD-104 and ANX007 could compete with IONIS-FB-L_{Rx}.

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 in the past disclosed that SPINRAZA revenue decreased 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 our commercial medicines 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 indication(s) in accordance with the approved label. The FDA and other regulatory authorities 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 authorities 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 CMOs 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.

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

We have entered into separate collaborative arrangements with Biogen to develop and commercialize SPINRAZA and QALSODY. We entered into these collaborations primarily to:

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

We are relying on Biogen to obtain additional regulatory approvals for SPINRAZA and QALSODY, generate additional clinical data for SPINRAZA and QALSODY, manufacture SPINRAZA and QALSODY, and successfully commercialize SPINRAZA and QALSODY. In general, we cannot control the amount and timing of resources that Biogen devotes to our collaborations. If Biogen fails to further develop SPINRAZA or QALSODY, obtain additional regulatory approvals for SPINRAZA or QALSODY, manufacture SPINRAZA or QALSODY, or successfully commercialize SPINRAZA or QALSODY, or if Biogen's efforts in any of these respects are ineffective, revenues for SPINRAZA or QALSODY would be negatively affected.

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

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

We have entered into a collaborative arrangement with AstraZeneca to develop and commercialize WAINUA. Under the terms of the collaboration agreement, we and AstraZeneca will co-develop and co-commercialize WAINUA in the U.S. and AstraZeneca will have the sole right to commercialize WAINUA in all other countries. 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 WAINUA is not successful for any reason, WAINUA may not meet our commercial objectives and our revenues for WAINUA 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 WAINUA 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 WAINUA.

If we are not successful in expanding our manufacturing capabilities or 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 need to optimize and manage large-scale commercial manufacturing capabilities either on a standalone basis or through a third-party manufacturer. As our drug development and commercial pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. While we believe our current capabilities and those we obtain through third-party manufacturers support our manufacturing needs now, it will be important to expand our manufacturing infrastructure in the future, which will likely require substantial expenditures. 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.

In addition, 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.

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 our commercial medicines and our medicines in development, or could result in enforcement action after authorization that might limit the commercial success of our medicines, including our commercial medicines and our medicines in development.

We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and WAINUA and drug product for WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities could limit the commercial success of our medicines.

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 our commercial medicines, 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 our commercial medicines 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 authorities will not approve our medicines for marketing or our commercial medicines in additional markets or for additional indications. If the FDA or another regulatory authority believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including our commercial medicines or our medicines in development, the authority will not approve the specific medicine or will require additional studies, which could be time consuming and expensive and 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 Notice of Non-Compliance Withdrawal Letter, or 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 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; 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 in development, or failure to receive additional marketing authorizations for our commercial medicines, or delays in these authorizations, could prevent or delay commercial introduction of the medicine, and, as a result, could negatively impact our ability to generate revenue from product sales.

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

Drug discovery and drug development have 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(s), 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 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 QALSODY did not meet the primary clinical endpoint in the Phase 3 VALOR study; however, trends favoring QALSODY 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.

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 or 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.

Further, the FDA or other regulatory authorities could request, among other things, 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. In addition, under accelerated approval the FDA is requiring completion of the ongoing Phase 3 trial for QALSODY to confirm the clinical benefit of QALSODY.

Moreover, our commercial medicines 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. Any failure or delay in our clinical studies could reduce the commercial potential or viability of our medicines.

We depend on third parties to conduct 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, Medpace, Inc., Parexel International Corporation, Syneos Health, Inc. and Thermo Fisher Scientific Inc. for the clinical studies for our medicines, including WAINUA for the treatment of ATTR-CM, donidalorsen, olezarsen, ulefnersen and zilganersen. 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, but we are responsible for ensuring that such investigators 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. For example, some of our key vendors have in the past experienced labor shortages, which impacted their ability to perform services for us for certain of our clinical trials. Subsequent failures of these third parties to carry out their obligations, or a termination of our relationship with such third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines.

In addition, while we do not have any clinical trial sites in Ukraine or Gaza, we do have a limited number of clinical trial sites in Russia and Israel that may be materially impacted by the ongoing wars between Russia and Ukraine and military conflicts in Israel and the surrounding areas, as well as related political or economic responses and counter-responses by various global actors, or collectively, conflicts in Eastern Europe and the Middle East, and could result in difficulties enrolling or completing our clinical trials in such areas on schedule. Furthermore, the U.S. and its European allies have imposed significant sanctions against Russia, including regional embargoes, full blocking sanctions, and other restrictions targeting major Russian financial institutions. The U.S. government has also indicated it will consider imposing additional sanctions and other similar measures in the future. Our ability to conduct clinical trials in Russia may become restricted under applicable sanctions laws, which would require us to identify alternative trial sites, and could increase our costs and delay the clinical development of certain of our medicines.

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 some 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 funding many of the medicines in our development pipeline. For example, we are relying on:

- AstraZeneca for the joint development and funding of WAINUA;
- Novartis for development and funding of pelacarsen;
- GSK for development and funding of bepirovirsen; and
- Roche for development and funding of IONIS-FB-L_{Rx}.

If any of these pharmaceutical companies stops developing and 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, in 2022, Pfizer and Bayer decided to discontinue the clinical development programs for vupanorsen and fesomersen, respectively.

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 and commercialize 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, Biogen, GSK, Novartis, Otsuka and Roche, these collaborations may not continue or result in commercialized medicines, or may not progress as quickly as we anticipated.

For example, a collaborator such as AstraZeneca, Biogen, GSK, Novartis, Otsuka 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 to 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 QALSODY, SPINRAZA, WAINUA, bepirovirsen, donidalorsen, IONIS-FB-L_{Rx} and pelacarsen.

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 olezarsen for the treatment of patients with FCS, to ulefnersen for the treatment of patients with FUS-ALS, and to ION582 for the treatment of patients with Angelman syndrome. The FDA and EMA have granted orphan drug designation to WAINUA for the treatment of patients with ATTR, to donidalorsen for the treatment of patients with HAE, to TEGSEDI for the treatment of patients with ATTRv-PN, to WAYLIVRA for the treatment of patients with FCS, to tominersen for the treatment of patients with HD, and to ION356 for the treatment of patients with Pelizaeus-Merzbacher disease. 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.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition

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 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. In addition, as we commercialize more medicines on our own, we will need to invest significant financial resources to continue developing the infrastructure required to successfully commercialize our medicines, including the expansion of our manufacturing capabilities. All of these activities will require significant cash. As of December 31, 2023, we had cash, cash equivalents and short-term investments equal to $2.3 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including our commercial medicines, 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:

- successful commercialization of our commercial medicines;
- the profile and launch timing of our medicines in development;
- 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 on acceptable terms or at all. 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, or commercial operations. 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.

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

Because drug discovery and development require 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, 2023, we had an accumulated deficit of approximately $1.8 billion and stockholders' equity of approximately $0.4 billion. Most of our income has historically come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. We will now and continuing into the foreseeable future need to invest significant financial resources to develop capabilities to commercialize medicines on our own and expect that our income in the future will be driven primarily by commercial sales. If we do not earn substantial revenue from commercial sales, we may incur additional operating losses in the future, which could restrict our ability to successfully develop additional medicines or sustain future profitability.

We may not be entitled to obtain additional milestone payments under our royalty monetization agreement with Royalty Pharma.

In January 2023, we entered into a Royalty Purchase Agreement with Royalty Pharma Investments. In addition to the $500 million we received at closing, this agreement makes available to us up to an additional $625 million in milestone payments. However, these additional milestone payments are subject to satisfaction of certain conditions related to the regulatory approval or commercial sales of pelacarsen, in certain cases by specific deadlines. Should we not satisfy such conditions by the applicable deadlines, or if we fail to meet our obligations or default under this agreement, the actual amount of additional payments to us could be substantially less than the maximum amounts available thereunder.

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, any of 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 our commercial medicines, 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 our commercial medicines or any of our 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 product liability

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 our commercial medicines 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.

Risks related to our personnel

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, and as we move towards commercializing medicines on our own, we will become increasingly dependent on the principal members of our commercial team. We do not have employment agreements with any of our employees that would prevent them from leaving us. The loss of our management, key scientific or commercial employees might slow the achievement of important research and development or commercial goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work and that we recruit and retain qualified marketing, sales, market access, distribution, and related personnel to commercialize our medicines. We may not be able to attract and retain skilled and experienced personnel on acceptable terms because of intense competition for experienced personnel among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies or in commercializing our medicines may make it more challenging to recruit and retain qualified personnel.

Risks related to pandemics, climate change and other events

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

Our business could be 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 disruption in the operations of third-party manufacturers and contract research organizations upon whom we rely. For example, enrollment in some of our clinical trials was delayed due to the COVID-19 pandemic.

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 currently manufacture most of our research and clinical supplies in a manufacturing facility located in Carlsbad, California. We manufacture the finished drug product for TEGSEDI, WAINUA and WAYLIVRA at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA and QALSODY. 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, wars, 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.

Risks related to cybersecurity, social media and artificial intelligence

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, particularly as companies (including us) moved to more remote work structures during and following the COVID-19 pandemic. In addition, the number and frequency of cybersecurity events globally may be heightened during times of geopolitical tension or instability between countries, including, for example, the ongoing conflicts in Eastern Europe and the Middle East.

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, delay progress on the development of our medicines, 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.

The increasing use of social media platforms and artificial intelligence based software presents new risks and challenges.

Social media is increasingly being used to communicate about our medicines and the diseases our therapies are designed to treat. Social media practices in the biopharmaceutical industry continue to evolve and regulations relating to such use are not always clear and create uncertainty and risk of noncompliance with regulations applicable to our business. There is also a risk of inappropriate disclosure of sensitive information or negative or inaccurate posts or comments about us on social media. We may also encounter criticism on social media regarding our company, management, or medicines. Our reputation could be damaged by negative publicity or if adverse information concerning us is posted on social media platforms or similar mediums, which we may not be able to reverse. If any of these events were to occur or we otherwise fail to comply with applicable regulations, we could incur liability, face restrictive regulatory actions or incur other harm to our business.

Additionally, the use of artificial intelligence, or AI, based software is increasingly being used in the biopharmaceutical industry. Use of AI based software may lead to the release of confidential proprietary information, which may impact our ability to realize the benefit of our intellectual property.

Risks related to our securities and the global credit markets

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. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to our commercial medicines and medicines in development, the price of our securities could decrease.

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, 2023, the closing market price of our common stock ranged from $52.27 to $32.69 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.

Broad market factors may materially harm the market price of our common stock irrespective of our operating performance. For example, recent events such as the COVID-19 pandemic, the ongoing conflicts in Eastern Europe and the Middle East, and the failure of Silicon Valley Bank have caused disruptions of global financial markets and resulted in increased volatility in the trading price of our common stock. In addition, industry factors may materially harm the market price of our common stock. Nasdaq, and the market for biotechnology companies in particular, have historically 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 that 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, bylaws, 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, chairperson 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 2023, we completed a $575 million offering of 1.75% Notes and used $488.2 million of the net proceeds from the issuance of the 1.75% Notes to repurchase $504.4 million of our 0.125% Notes. In 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 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, as of December 31, 2023, we may issue approximately 28.2 million shares of our common stock upon conversion of our 1.75% Notes, 0% Notes and 0.125% Notes. In connection with the issuance of the 0% Notes and 0.125% Notes, we entered into certain call spread transactions covering 10.9 million shares and 6.6 million shares, respectively, that we expect will offset the dilution to holders of common stock upon any conversion of those notes. In addition, of the shares reserved, 6.1 million shares are reserved for issuance upon conversion of 0.125% Notes that we have repurchased and are currently held by us in treasury (and thus would not be dilutive). As a result, to the extent we elect to convert the 0.125% Notes held by us in treasury, we expect we would receive up to 6.1 million shares upon settlement of related convertible note hedges (without any additional dilution caused by the conversion of the 0.125% Notes held in treasury). However, the anti-dilutive effect of the convertible note hedges is offset by certain warrant transactions we entered into in connection with the issuance of the 0% Notes and the 0.125% Notes. 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.

Negative conditions in the global credit markets and financial services and other industries may adversely affect our business, financial condition or stock price.

The global credit and financial markets have experienced extreme volatility and disruptions recently, including as a result of the COVID-19 pandemic, ongoing conflicts in Eastern Europe and the Middle East, and the failure of Silicon Valley Bank. These disruptions can result in severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our operations, growth plans, financial performance or stock price. In addition, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all.

A variety of risks associated with operating our business and marketing our medicines internationally could adversely affect our business. In addition to our U.S. operations, we are commercializing TEGSEDI in the EU, 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 and export 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, 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.

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 contract research organizations, contract manufacturing organizations, distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. Importantly, 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.

Risks related to compliance with laws

Our operations are subject to extensive legal and regulatory requirements affecting the health care industry.

Our operations are subject to extensive legal and regulatory requirements affecting the health care industry, 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. 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.

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 for pollution liability in amounts and types that we consider commercially reasonable, 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 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 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. In July 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted, and in August 2022, the SEC adopted additional rules and regulations under the Dodd-Frank Act related to "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 has and may in the future lead to additional compliance costs and impact the manner in which we operate our business.

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 carry forward 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 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 our merger with Akcea Therapeutics, Inc. in 2020, or 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 NOLs 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.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 1C. Cybersecurity

Risk management and strategy

We have implemented and maintain various information security processes designed to detect, respond to, recover, and protect our technology ecosystem from cybersecurity threats. These processes are designed to identify, assess, and manage material risks that may result from cybersecurity threats and apply to our critical technologies inclusive of networks, third party hosted services, communications systems, hardware, software, and critical data, including intellectual property and confidential information that is proprietary, strategic, or competitive in nature.

Our Information Technology department, led by our Senior Vice President, Information Technology, helps to detect, respond to, and manage cybersecurity threats and risks by monitoring and evaluating our threat environment using various manual and automated tools in certain environments and systems and other methods including, for example:

- analyzing reports of certain threats and actors;
- conducting scans of the threat environment;
- evaluating our and our industry's risk profile;
- evaluating certain threats reported to us;
- conducting internal and external audits;
- conducting threat assessments for certain internal and external threats; and
- conducting vulnerability assessments to identify vulnerabilities.

Depending on the environment and system, we have implemented and maintain various technical, physical, and organizational measures, processes, standards, and policies designed to manage and mitigate material risks from cybersecurity threats to our critical technologies, including, for example:

- incident response plan;
- disaster recovery/business continuity plans;
- risk assessments;
- encryption of certain data;
- network security and access controls for certain systems;
- physical security;
- asset management, tracking and disposal;
- systems monitoring; and
- employee training.

Our assessment and management of material risks from cybersecurity threats are integrated into the Company's overall risk management processes. For example, cybersecurity risk is assessed as a component of the Company's enterprise risk management program. In addition, we have developed a process whereby our senior management will evaluate material risks from cybersecurity threats against our overall business objectives and will report certain cybersecurity incidents to the Audit Committee of the Board of Directors, which evaluates our overall enterprise risk.

We use third-party service providers to perform various functions throughout our business, such as application providers and hosting companies. We use third-party service providers to assist us from time to time to identify, assess, and manage material risks from cybersecurity threats, including, for example, legal counsel, cybersecurity consultants, cybersecurity software providers, penetration testing firms, and forensic investigators.

For a description of the risks from cybersecurity threats that may materially affect the Company and how they may do so, see our risk factors under Part 1. Item 1A. Risk Factors in this Annual Report on Form 10-K, including the risk factor titled "*We are dependent on information technology systems, infrastructure and data, which exposes us to data security risks*."

Governance

Our Board of Directors addresses the Company's cybersecurity risk management as part of its general oversight function. The Audit Committee of the Board of Directors is responsible for overseeing the Company's cybersecurity risk management processes, including oversight and mitigation of risks from cybersecurity threats.

Our cybersecurity risk assessment and management processes are implemented and maintained by our Senior Vice President, Information Technology, who is an information technology professional with healthcare and digital certifications and has over 25 years of relevant experience, and other employees in our Information Technology department who are certified security professionals and have relevant experience.

Our Senior Vice President, Information Technology is responsible for hiring appropriate personnel, helping to integrate cybersecurity risk considerations into the Company's overall risk management strategy, communicating key priorities to relevant personnel, helping prepare for cybersecurity incidents, approving cybersecurity processes, and reviewing security assessments and other security-related reports.

Our cybersecurity incident response plan is designed to escalate cybersecurity incidents, depending on the circumstances, to our senior management team and Audit Committee of the Board of Directors. As part of such process, the Audit Committee of the Board of Directors receives regular reports from our Senior Vice President, Information Technology concerning the Company's significant cybersecurity threats and risks and the processes the Company has implemented to address them.

Item 2. Properties

As of February 15, 2024, 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	176,300	Leased	2037	Two, five-year options to extend
Office and meeting space facility	Carlsbad, CA	74,000	Leased	2037	Two, five-year options to extend
Manufacturing facility	Carlsbad, CA	26,800	Owned		
Manufacturing support facility	Carlsbad, CA	25,800	Leased	2026	One, five-year option to extend
Office space facility	Boston, MA	14,300	Leased	2029	One, five-year option to extend
Office space facility	Carlsbad, CA	5,800	Leased	2027	None
Warehouse facility	Carlsbad, CA	4,200	Leased	2028	None
Office space facility	Dublin, Ireland	3,900	Leased	2025	None
		331,100			

We believe that our current and future facilities will be adequate for the foreseeable future. Refer to Part IV, Section 15, Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for details on real estate transactions.

Item 3. Legal Proceedings

For details of legal proceedings, refer to Part IV, Item 15, Note 11, *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

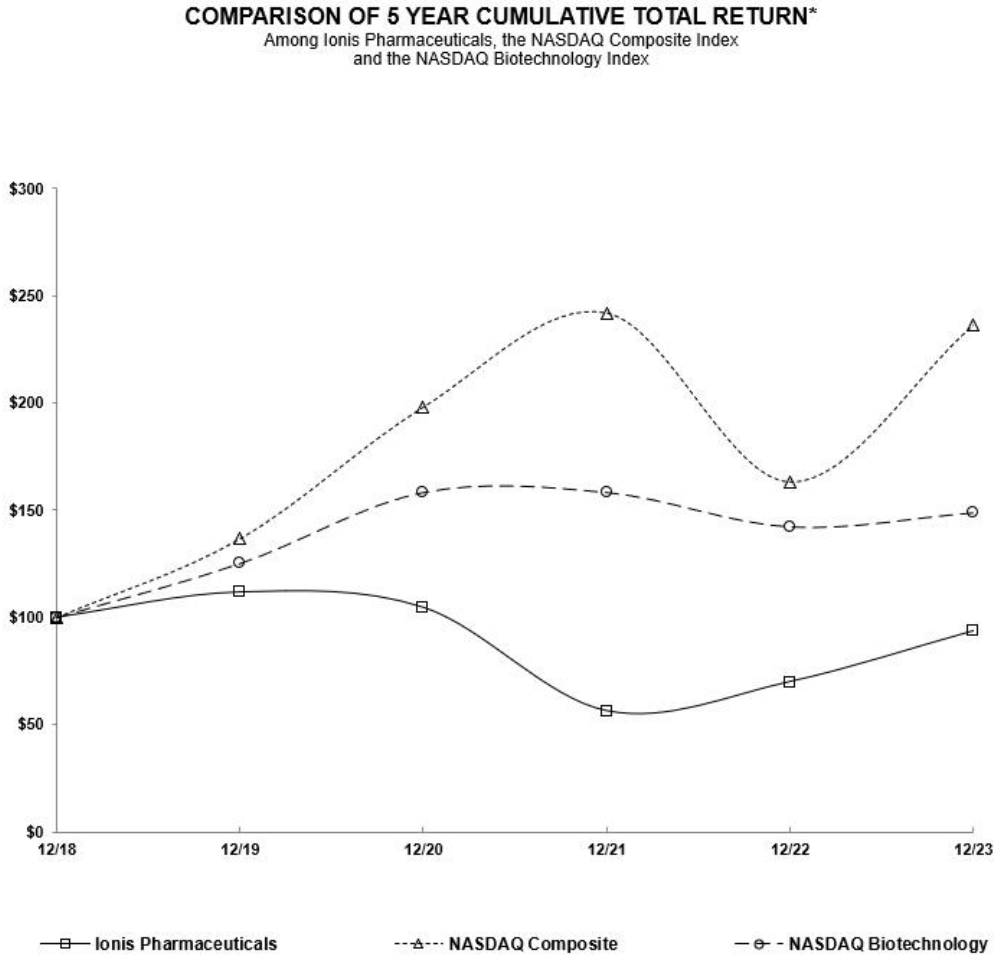
Market Information and Dividends

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "IONS." As of February 15, 2024, there were approximately 476 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, 2018 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, 2018 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-18	Dec-19	Dec-20	Dec-21	Dec-22	Dec-23
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 111.75	$ 104.59	$ 56.29	$ 69.87	$ 93.58
Nasdaq Composite Index	$ 100.00	$ 136.69	$ 198.10	$ 242.03	$ 163.28	$ 236.17
Nasdaq Biotechnology Index	$ 100.00	$ 125.11	$ 158.17	$ 158.20	$ 142.19	$ 148.72

(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. Reserved

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, 2023, and our financial condition as of December 31, 2023. Refer to our 2022 Form 10-K for our results of operations for 2022 compared to 2021. 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 included in Item 8 of Part II of this report.

Overview

As noted in our Business Overview in Part I of this report, for three decades, we have invented medicines that we believe bring better futures to people with serious diseases. Today, as a pioneer in RNA-targeted medicines, we continue to drive innovation in RNA therapies. We currently have five marketed medicines: SPINRAZA, QALSODY, WAINUA, TEGSEDI and WAYLIVRA. We also have a rich innovative late- and mid-stage pipeline in neurology, cardiology and other areas of high patient need. We currently have nine medicines in Phase 3 development and multiple additional medicines in early and mid-stage development. Refer to Part I, Item 1, *Business*, for further details on our business and key developments in our medicines.

Results of Operations

Below we have included our results of operations for 2023 compared to 2022. Refer to our 2022 Form 10-K for our results of operations for 2022 compared to 2021. The following table provides selected summary information from our consolidated statements of operations for 2023 and 2022 (in millions):

	Year Ended December 31,	
	2023	2022
Total revenue	$ 787.6	$ 587.4
Total operating expenses	$ 1,141.4	$ 997.6
Loss from operations	$ (353.7)	$ (410.2)
Net loss	$ (366.3)	$ (269.7)
Cash, cash equivalents and short-term investments	$ 2,331.2	$ 1,986.9

Revenue

Total revenue for 2023 was $787.6 million compared to $587.4 million in 2022 and was comprised of the following (in millions):

	Year Ended December 31,	
	2023	2022
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$ 240.4	$ 242.3
Other commercial revenue:		
TEGSEDI and WAYLIVRA revenue, net	34.9	30.1
Licensing and other royalty revenue	33.3	31.0
Total other commercial revenue	68.2	61.1
Total commercial revenue	308.6	303.4
R&D revenue:		
Amortization from upfront payments	125.3	68.6
Milestone payments	100.5	74.0
License fees	116.8	37.0
Other services	10.0	27.6
Collaborative agreement revenue	352.6	207.2
WAINUA joint development revenue	126.4	76.8
Total R&D revenue	479.0	284.0
Total revenue	$ 787.6	$ 587.4

Commercial revenues in 2023 were relatively consistent compared to 2022. Commercial revenue for 2023 included $240 million from SPINRAZA royalties, which were relatively consistent compared to 2022. Our commercial revenue in 2023 also included royalties from QALSODY U.S. product sales.

Our R&D revenue increased in 2023 compared to 2022 primarily due to continued success with our pipeline and technology. As a result, we earned significant partner payments, including $50 million from AstraZeneca for the FDA approval of WAINUA for ATTRv-PN in the U.S., $36 million from AstraZeneca for licensing ION826 and payments from our new collaborations with Otsuka, Roche and Novartis.

WAINUA (Eplontersen) Collaboration with AstraZeneca

Our financial results for the years ended December 31, 2023 and 2022 reflected the cost-sharing provisions related to our collaboration with AstraZeneca to develop and commercialize WAINUA for the treatment of ATTR. Under the terms of the collaboration agreement, AstraZeneca is currently paying 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading and conducting the Phase 3 development program, we are recognizing as R&D revenue the 55 percent of cost-share funding AstraZeneca is responsible for, net of our share of AstraZeneca's development expenses, in the same period we incur the related development expenses.

As AstraZeneca is responsible for the majority of the medical affairs and commercial costs in the U.S. and all costs associated with bringing WAINUA to market outside the U.S., we are recognizing cost-share funding we receive from AstraZeneca related to these activities as a reduction of our medical affairs and commercialization expenses, which we classify as R&D and selling, general and administrative, or SG&A, expenses, respectively. We expect our medical affairs and commercialization expenses to increase as WAINUA advances toward the market under our collaboration with AstraZeneca.

The following table sets forth information on revenue and expenses under this collaboration (in millions):

	Year Ended December 31,	
	2023	2022
WAINUA joint development revenue	$ 126.4	$ 76.8
Research and development expenses related to Phase 3 development expenses for WAINUA	150.8	147.1
Medical affairs expenses for WAINUA	4.1	2.0
Commercialization expenses for WAINUA	15.6	2.6

Our WAINUA joint development revenue in 2023 includes a $50 million milestone payment from AstraZeneca that we earned when the FDA approved WAINUA for ATTRv-PN in the U.S.

Operating Expenses

The following table sets forth information on operating expenses (in millions):

	Year Ended December 31,	
	2023	2022
Operating expenses, excluding non-cash compensation expense related to equity awards	$ 1,035.7	$ 897.3
Non-cash compensation expense related to equity awards	105.7	100.3
Total operating expenses	$ 1,141.4	$ 997.6

Our operating expenses, excluding non-cash compensation expense related to equity awards, increased in 2023 compared to 2022, primarily due to certain one-time costs, including a non-cash charge associated with a lease exit and the license fee we paid to Vect-Horus. Our R&D expenses increased as we advanced our pipeline, which included an increase in the costs associated with our clinical studies as most of our Phase 3 studies were either fully enrolled or approaching full enrollment at the end of 2023. Our SG&A expenses increased due to expenses related to our launch preparation activities for WAINUA, olezarsen and donidalorsen.

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 is comprised of costs related to our commercial revenue, which 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.

The following table sets forth information on cost of sales (in millions):

	Year Ended December 31,	
	2023	2022
Cost of sales, excluding non-cash compensation expense related to equity awards	$ 8.7	$ 13.4
Non-cash compensation expense related to equity awards	0.4	0.7
Total cost of sales	$ 9.1	$ 14.1

Research, Development and Patent Expenses

Our research, development and patent expenses consist of expenses for drug discovery, drug development, medical affairs, 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,	
	2023	2022
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 821.7	$ 759.4
Non-cash compensation expense related to equity awards	77.9	73.7
Total research, development and patent expenses	$ 899.6	$ 833.1

Drug Discovery

We use our proprietary technologies 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 drug discovery research, and that of our partners. Drug discovery is also the function that is responsible for advancing our core technology. This function is also responsible for making investments in complementary technologies to expand the reach of our technologies.

The following table sets forth information on drug discovery expenses (in millions):

	Year Ended December 31,	
	2023	2022
Drug discovery expenses, excluding non-cash compensation expense related to equity awards	$ 125.6	$ 181.3
Non-cash compensation expense related to equity awards	16.2	16.2
Total drug discovery expenses	$ 141.8	$ 197.5

Drug discovery expenses, excluding non-cash compensation expense related to equity awards, decreased in 2023 compared to 2022. In 2022, we recognized $80 million for licensing Metagenomi's gene editing technologies.

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,	
	2023	2022
WAINUA	$ 115.5	$ 103.9
TEGSEDI and WAYLIVRA	8.1	10.6
Olezarsen	138.3	68.1
Donidalorsen	24.9	14.1
Zilganersen	8.4	5.6
Ulefnersen	10.8	8.4
Other development projects	101.0	123.5
Development overhead expenses	123.3	92.0
Total drug development, excluding non-cash compensation expense related to equity awards	530.3	426.2
Non-cash compensation expense related to equity awards	34.5	31.5
Total drug development expenses	$ 564.8	$ 457.7

Our development expenses, excluding non-cash compensation expense related to equity awards, increased in 2023 compared to 2022 primarily due to our advancing late-stage pipeline and full or nearly full enrollment of many of our Phase 3 studies.

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. Because we always have numerous medicines in preclinical and varying stages of 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.

Medical Affairs

Our medical affairs function is responsible for funding and coordinating investigator-sponsored trials, communicating scientific and clinical information to healthcare providers, medical professionals and patients, and managing publications.

The following table sets forth information on medical affairs expenses (in millions):

	Year Ended December 31,	
	2023	2022
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$ 19.5	$ 15.9
Non-cash compensation expense related to equity awards	3.4	2.0
Total medical affairs expenses	$ 22.9	$ 17.9

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, increased in 2023 compared to 2022 as we continued advancing our late-stage pipeline.

Manufacturing and Development Chemistry

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

The following table sets forth information on manufacturing and development chemistry expenses (in millions):

	Year Ended December 31,	
	2023	2022
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$ 65.3	$ 76.2
Non-cash compensation expense related to equity awards	8.8	9.9
Total manufacturing and development chemistry expenses	$ 74.1	$ 86.1

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, decreased in 2023 compared to 2022. In 2022, we manufactured higher quantities of API to support launch preparation activities for WAINUA, olezarsen and donidalorsen. Refer to the section titled, *Manufacturing*, in Part I, Item 1, *Business*, for further details on the activities and types of costs we incur in our manufacturing process.

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, information technology 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,	
	2023	2022
Personnel costs	$ 27.2	$ 21.2
Occupancy	28.7	19.2
Consulting	4.8	0.8
Patent expenses	4.3	4.7
Insurance	3.6	3.8
Computer software and licenses	2.7	1.9
Other	9.7	8.2
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	81.0	59.8
Non-cash compensation expense related to equity awards	15.0	14.1
Total R&D support expenses	$ 96.0	$ 73.9

R&D support expenses, excluding non-cash compensation expense related to equity awards, increased in 2023 compared to 2022. The increase was primarily related to increased occupancy, personnel and consulting costs to support advancing our pipeline and our technology. In October 2022, we executed a sale and leaseback transaction for our headquarters in Carlsbad, California. As a result, beginning in the fourth quarter of 2022, our occupancy costs increased because we began incurring rent expense for these facilities.

Selling, General and Administrative Expenses

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 SG&A 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 and QALSODY.

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

	Year Ended December 31,	
	2023	2022
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$ 205.1	$ 124.4
Non-cash compensation expense related to equity awards	27.5	25.9
Total selling, general and administrative expenses	$ 232.6	$ 150.3

SG&A expenses, excluding non-cash compensation expense related to equity awards, increased in 2023 compared to 2022 primarily due to increased expenses related to our go-to-market activities for WAINUA, olezarsen and donidalorsen. In addition, we recorded a one-time expense of $20 million when we terminated a build-to-suit lease agreement in August 2023. Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for further details on the lease termination.

Investment Income

Investment income for 2023 was $89.0 million compared to $25.3 million for 2022. The increase in investment income was primarily due to an increase in interest rates associated with our investments in debt securities and an increase in our cash available for investment during 2023 compared to 2022. Our cash balance increased due to the $500.0 million upfront payment we received in January 2023 from our royalty purchase agreement with Royalty Pharma Investments, or Royalty Pharma, net proceeds we received from the debt offering in June 2023 and payments from partners. These increases were partially offset by the repurchase of $504.4 million in principal of our 0.125% Notes during 2023.

Interest Expense

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

	Year Ended December 31,	
	2023	2022
Convertible senior notes:		
Non-cash amortization of debt issuance costs	$ 5.9	$ 5.3
Interest expense payable in cash	6.4	0.7
Interest on mortgage for primary R&D and manufacturing facilities	0.4	2.1
Total interest expense	$ 12.7	$ 8.1

In 2023, we completed a $575.0 million offering of our 1.75% Notes and repurchased $504.4 million in principal of our 0.125% Notes. As a result, beginning in the second quarter of 2023, our interest expense related to our convertible notes increased because we began incurring interest expense for our 1.75% Notes.

Interest Expense Related to Sale of Future Royalties

We recorded $68.8 million of interest expense related to the sale of future royalties in 2023 as a result of the Royalty Pharma transaction, in which we sold a minority interest in our future SPINRAZA and pelacarsen royalties to Royalty Pharma for a $500 million upfront payment and $625 million of potential future payments. Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for further details.

Loss on Investments

We recorded a $1.9 million and $7.3 million loss on investments for 2023 and 2022, respectively. The period-over-period fluctuation in our loss on investments was primarily driven by changes in the fair value of our investments in publicly traded and privately held biotechnology companies.

Gain on Sale of Real Estate

In 2022, we closed a purchase and sale agreement with a real estate investor in which we sold and leased back the facilities at our headquarters location in Carlsbad, California for a total purchase price of $263.4 million and recorded a gain of $150.1 million in 2022, resulting in income tax expense of $8.8 million. Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, for further details on this transaction.

Other Income (Expense)

In 2023, we completed a $575.0 million offering of our 1.75% Notes and used $488.2 million of the net proceeds to repurchase $504.4 million in principal of our 0.125% Notes. As a result of these repurchases, we recorded a $13.4 million gain on early retirement of debt in 2023, which reflects the difference between the amounts we paid to repurchase portions of our 0.125% Notes and the net carrying balance of the liability at the time that we repurchased the debt. Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for further details regarding our convertible debt.

Income Tax Expense (Benefit)

We recorded an income tax expense of $32.3 million for 2023 compared to $11.7 million for 2022.

The primary drivers of our income tax expense despite our full year pretax loss relate to the requirement for taxpayers to amortize research and development expenditures over five years pursuant to Internal Revenue Code, or IRC, Section 174 beginning in 2022 under the Tax Cuts and Jobs Act of 2017, or TCJA, and the impact of the royalty purchase agreement with Royalty Pharma, which we reflected as a taxable sale which required us to include the proceeds from the sale, net of currently deductible issuance costs, as taxable income in 2023. The resulting tax liability is partially offset by the utilization of our R&D tax credits.

The increase in income tax expense for 2023 compared to 2022 relates primarily to the impact of the Royalty Pharma transaction.

We continue to maintain a full valuation allowance on all our net deferred tax assets.

Net Loss and Net Loss per Share

We generated a net loss of $366.3 million for 2023 compared to $269.7 million for 2022. Our net loss increased for 2023 compared to 2022 primarily due to factors discussed in the sections above. Basic and diluted net loss per share for 2023 were $2.56 compared to $1.90 for 2022.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also financed our operations from commercial revenue from SPINRAZA and QALSODY royalties and TEGSEDI and WAYLIVRA commercial revenue. In addition, we expect to receive commercial revenue from WAINUA royalties beginning in 2024. From our inception through December 31, 2023, we have earned approximately $7.2 billion in revenue. We have also financed our operations through the sale of our equity securities, the issuance of long-term debt and the sale of future royalties. From the time we were founded through December 31, 2023, we have raised net proceeds of approximately $2.1 billion from the sale of our equity securities. Additionally, from our inception through December 31, 2023, we have borrowed approximately $2.7 billion under long-term debt arrangements and received proceeds of $0.5 billion from the sale of future royalties to finance a portion of our operations.

Our cash, cash equivalents and short-term investments, working capital and long-term obligations increased from 2022 to 2023. As discussed above, in 2023, we repurchased $504.4 million in principal of our 0.125% Notes. In the third quarter of 2023, we closed a real estate transaction and received $32.4 million. In the second quarter of 2023, we issued $575.0 million of 1.75% Notes (due in June 2028). In the first quarter of 2023, we received an upfront payment of $500.0 million when we entered into a royalty purchase agreement with Royalty Pharma and recorded a corresponding long-term liability related to the sale of future royalties.

The following table summarizes our contractual obligations, excluding our liability related to the sale of future royalties, as of December 31, 2023. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements.

Contractual Obligations	**Payments Due by Period (in millions)**		
(selected balances described below)	**Total**	**Less than 1 year**	**More than 1 year**
1.75% Notes (principal and interest payable)	$ 620.3	$ 10.1	$ 610.2
0% Notes (principal payable)	632.5	—	632.5
0.125% Notes (principal and interest payable)	44.6	44.6	—
Building mortgage payments (principal and interest payable)	10.2	0.5	9.7
Operating leases	279.5	20.4	259.1
Other obligations (principal and interest payable)	0.8	0.1	0.7
Total	$ 1,587.9	$ 75.7	$ 1,512.2

Our contractual obligations consist primarily of our convertible debt. In addition, we also have a facility mortgage, facility leases, equipment financing arrangements and other obligations. We believe our cash, cash equivalents and short-term investments, as well as plans for cash in the future, will be sufficient to fund our planned operations and these obligations. 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 Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, and Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for the significant terms of each convertible debt instrument.

Operating Facilities

Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for further details on our operating facilities.

Operating Leases

Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for further details on our operating leases.

Royalty Revenue Monetization

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our agreements with Biogen and Novartis, respectively. Refer to Part IV, Item 15, Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for further details on this agreement.

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2023 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, securing lines of credit or executing royalty monetization agreements. 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.

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 Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements.

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

- Assessing the propriety of revenue recognition and associated deferred revenue;
- Determining the appropriate cost estimates for unbilled preclinical studies and clinical development activities; and
- Assessing the appropriate estimate of anticipated future royalty payments under our royalty purchase agreement

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 Accounting Standards Codification, or ASC, Topic 808, *Collaborative Arrangements*, or 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 are therefore within the scope of ASC 606, *Revenue from Contracts with Customers*. 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.

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

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 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.

- 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 that are recognized immediately or amortized over the period in which we satisfy our performance obligation. Each of these types of revenue require us to make various judgements and estimates.

R&D Services with 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 amount of effort it will take us to complete our R&D services performance obligation. If we change our estimates, we may have to adjust our revenue.

Milestone Payments

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

- Whether a milestone payment is probable (discussed in detail above under “Determining the transaction price, including any variable consideration”);
- Whether a 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 “R&D Services with Upfront Payments”); and
- 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. Refer to Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements 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, 2023, a hypothetical 10 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 of approximately $10.6 million.

Liability Related to Sale of Future Royalties

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our agreements with Biogen and Novartis, respectively. Under our agreement with Royalty Pharma, we calculate the liability related to the sale of future royalties, effective interest rate and the related interest expense using our current estimate of anticipated future royalty payments under the arrangement, which we periodically reassess based on internal projections and information from our partners who are responsible for commercializing the medicines. The amount that Royalty Pharma will receive under the agreement is based on sales of SPINRAZA, our currently commercialized medicine, and pelacarsen, a product candidate that is not currently commercialized. As such, the repayment amounts that we estimate related to projections of future pelacarsen revenues contain more subjective estimation which we believe could lead to larger changes in estimates in the future. If there is a material change in our estimate, we will prospectively adjust the effective interest rate and the related interest expense.

There are numerous factors, most of which are not within our control, that could materially impact the amount and timing of future royalty payments, particularly those from Novartis for pelacarsen, and could result in changes to our estimate of future royalty payments to Royalty Pharma. Such factors include, but are not limited to, the regulatory approval and commercial sales of pelacarsen, competing products or other significant events. These factors and other events or circumstances could result in reduced royalty payments from sales of pelacarsen, which would result in a reduction of our non-cash royalty revenue and non-cash interest expense over the life of the agreement. Conversely, if sales of pelacarsen are more than amounts we estimated, the non-cash royalty revenue and non-cash interest expense we record would be greater over the life of the arrangement.

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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, 2023 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 evaluated 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, 2023.

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, 2023, 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, 2023.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2023, 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, 2023, 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, 2023, 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, 2023 and 2022, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2023, and the related notes and our report dated February 21, 2024 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 21, 2024

Item 9B. Other Information

Trading Plans

During the quarter ended December 31, 2023, our officers and directors (as defined in Rule 16a-1(f) under the Exchange Act), or Section 16 officers and directors, adopted or terminated contracts, instructions or written plans for the purchase or sale of our securities as noted in the table below.

* Contract, instruction or written plan intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) under the Exchange Act.
** "Non-Rule 10b5-1 trading arrangement" as defined in item 408(c) of Regulation S-K under the Exchange Act.

			Trading Arrangement			
	Action	Date	Rule 10b5-1*	Non-Rule 10b5-1**	Total Shares to be Sold	Expiration Date
Joseph Wender, Board Member	Adoption	November 30, 2023	X		104,079	February 28, 2025

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, 2023, 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 make all required disclosures regarding any amendments to, or waivers from, provisions of 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, 2023.

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)	14,090,732	$ 48.43	9,976,286(b)
Total	14,090,732	$ 48.43	9,976,286

(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, 386,792 were available for purchase under the ESPP as of December 31, 2023.

For additional details about our equity compensation plans, including a description of each plan, refer to Part IV, Item 15, Note 8, *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 "Information Regarding the Board and Corporate Governance" 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	Description of the Registrant's Securities, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference.
4.2	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.
4.3	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.
4.4	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	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.
4.6	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.
4.7	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.
4.8	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.
4.9	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.
4.10	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.
4.11	Indenture, dated as of June 12, 2023, by and between the Registrant and U.S. Bank Trust Company, a National Association, as trustee, including Form of 1.75 percent Global Note due in 2028, filed as an exhibit to the Registrant's Current Report on Form 8-K filed June 12, 2023 and incorporated herein by reference.
10.1*	Second Amended Non-Employee Director Compensation Policy, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 and incorporated herein by reference.
10.2*	Registrant's Amended and Restated Severance Benefit Plan dated March 17, 2022, filed as an exhibit to the Registrant's Quarterly Report on form 10-Q for the quarter ended March 31, 2022 and incorporated herein by reference.
10.3	Form of Indemnity Agreement entered into between the Registrant and its Directors and Executive Officers with related schedule
10.4	Form of Employee Confidential Information and Inventions Agreement, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
10.5*	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.
10.6*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 and incorporated herein by reference.
10.7*	Form of Option Agreement for Options granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.

10.8*	Forms of Restricted Stock Unit Grant Notice and Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 and incorporated herein by reference.
10.9*	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.
10.10*	Form of Option Agreement under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.
10.11*	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 Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.
10.12*	Forms of Performance Based Restricted Stock Unit Grant Notice and Performance Based Restricted Stock Unit Agreement for Performance Based Restricted Stock Units granted prior to January 1, 2023 under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference.
10.13*	Forms of Performance Based Restricted Stock Unit Grant Notice and Performance Based Restricted Stock Unit Agreement for Performance Based Restricted Stock Units granted beginning January 1, 2023 under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.
10.14*	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.
10.15*	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.
10.16*	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.
10.17*	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.
10.18	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.
10.19	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.
10.20	Purchase and Sale Agreement between Ionis Gazelle, LLC and 2850 2855 & 2859 Gazelle Owner (DE) LLC dated as of October 20, 2022, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.21	Purchase and Sale Agreement between the Registrant and Oxford I Asset Management USA Inc. dated as of October 20, 2022, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.22	First Amendment dated June 15, 2023 to the Purchase and Sale Agreement by and between the Registrant and Oxford I Asset Management USA Inc. dated as of October 20, 2022, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2023 and incorporated herein by reference.
10.23	Lease Agreement dated October 20, 2022 between the Registrant and 2850 2855 & 2859 Gazelle Owner (DE) LLC, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.24	Amended and Restated Lease Agreement between the Registrant and Lots 21 & 22 Owner (DE) LLC dated as of August 21, 2023, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.

10.25	First Amendment dated as of November 6, 2023 to Amended and Restated Lease Agreement between the Registrant and Lots 21 & 22 Owner (DE) LLC dated as of August 21, 2023.
10.26	Defeasance Pledge and Security Agreement dated as of October 20, 2022 by and among 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, and U.S. Bank Trust Company, National Association, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.27	Defeasance Assignment, Assumption and Release Agreement dated as of October 20, 2022 by and among Ionis Gazelle, LLC, DHC UBSCM 17 C3 Successor Borrower-R, 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, Midland Loan Services, a division of PNC Bank, National Association, and U.S. Bank Trust Company, National Association, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.
10.28	Defeasance Account Agreement dated as of October 20, 2022 by and among Ionis Gazelle, LLC, U.S. Bank Trust Company, National Association, U.S. 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, and Midland Loan Services, a division of PNC Bank, National Association, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.29	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.
10.30	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.
10.31	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.
10.32	Amendment #2 to the Research, Development and License Agreement by and between the Registrant and Glaxo Group Limited dated October 30, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.33	Amendment No. 3 to the Research, Development and License Agreement by and between the Registrant and Glaxo Group Limited dated July 10, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.34	Amendment #4 to the Research, Development and License Agreement by and between the Registrant and Glaxo Group Limited dated April 10, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.35	Amendment #5 to the Research, Development and License Agreement by and between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.36	Amendment #6 to Research, Development and License Agreement by and 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.
10.37	Amendment #7 to the Research, Development and License Agreement by and between 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.

10.38	Amendment #8 to the Research, Development and License Agreement by and 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) the type that the Registrant treats as private or confidential.
10.39	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.
10.40	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.
10.41	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.
10.42	Amendment #1 to the Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated December 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.43	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.
10.44	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.
10.45	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.
10.46	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.
10.47	Amendment No. 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.
10.48	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 March 31, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.49	Amendment #1 to HTT Research, Development, Option and License Agreement between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. dated January 9, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.50	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.

10.51	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.
10.52	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.
10.53	Amendment No. 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.
10.54	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) is the type that the Registrant treats as private or confidential.
10.55	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) the type that the Registrant treats as private or confidential.
10.56	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.
10.57	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.
10.58	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.
10.59	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.
10.60	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.
10.61	Amendment No. 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) the type that the Registrant treats as private or confidential.
10.62	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) the type that the Registrant treats as private or confidential.
10.63	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.

10.64	First Amendment dated July 8, 2022 to 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 Quarterly Report on Form 10-Q for the quarter ended June 30, 2022. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.65	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.
10.66	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.
10.67	Amendment No. 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.
10.68	Collaboration and License Agreement by and between the Registrant and Novartis Pharma AG dated as of August 2, 2023, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.69	Research, Development, and License Agreement by and among the Registrant, F. Hoffmann-La Roche Ltd., and Hoffmann-La Roche Inc. dated as of September 26, 2023, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.70	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) the type that the Registrant treats as private or confidential.
10.71	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) the type that the Registrant treats as private or confidential.
10.72	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, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.73	Amendment No. 2 dated July 28, 2022 to the 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, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.74	Amendment No. 3 dated April 27, 2023 to the 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 June 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.75	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) the type that the Registrant treats as private or confidential.
10.76	Collaboration and License Agreement by and between Akcea Therapeutics, Inc. and AstraZeneca AB dated December 6, 2021, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.

10.77	Letter Agreement dated June 29, 2023 in reference to the Collaboration and License Agreement dated December 6, 2021 by and between Akcea Therapeutics, Inc. and AstraZeneca AB, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.78	Collaboration and License Agreement between the Registrant and Metagenomi, Inc. dated November 10, 2022, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.79	Royalty Purchase Agreement by and between the Registrant, Akcea Therapeutics, Inc. and Royalty Pharma Investments 2019 ICAV dated as of January 9, 2023, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.80	License Agreement by and between the Registrant and Otsuka Pharmaceuticals Co., LTD. dated as of December 15, 2023. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
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.
97	Registrant's Amended and Restated Clawback Policy
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2023, 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 21st day of February, 2024.

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 21, 2024
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 21, 2024
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Chairman of the Board	February 21, 2024
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 21, 2024
/s/ ALLENE M. DIAZ Allene M. Diaz	Director	February 21, 2024
/s/ MICHAEL HAYDEN Michael Hayden, CM OBC MB ChB PhD FRCP(C) FRSC	Director	February 21, 2024
/s/ JOAN E. HERMAN Joan E. Herman	Director	February 21, 2024
/s/ JOSEPH KLEIN Joseph Klein, III	Director	February 21, 2024
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director	February 21, 2024
/s/ JOSEPH H. WENDER Joseph H. Wender	Lead Independent Director	February 21, 2024
/s/ MICHAEL YANG Michael Yang	Director	February 21, 2024

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, 2023 and 2022, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2023, 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, 2023 and 2022, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2023, 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, 2023, 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 21, 2024 expressed an unqualified opinion thereon.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures 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 separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Estimated Liability for Clinical Development Costs

Description of the Matter

As of December 31, 2023, the Company accrued $106 million for clinical development expenses. As discussed in Note 1 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 third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. The Company estimates its liability using assumptions about study and patient activities and the related expected expenses for those activities based on the contracted fees with service providers.

Auditing the Company's accruals for clinical and contract research organization 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 expenses. 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 expenses, 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 expenses 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 expenses and compared the results to the current year accrual.

Accounting for the Royalty Pharma Sale of Future Royalties Transaction

Description of the Matter

As discussed in Note 7 to the consolidated financial statements, in January 2023, the Company entered into a royalty purchase agreement to monetize a portion of future SPINRAZA and pelacarsen royalties that the Company is entitled to under existing agreements. As a result, the Company received an upfront payment of $500 million. The Company accounted for the sale of future royalties as a liability. The Company determines the effective interest rate used to record interest expense based on the estimate of future royalty payments over the term of the agreement. The carrying value of the liability related to the sale of future royalties at December 31, 2023 was $514 million.

Auditing the Company's liability related to the sale of future royalties was complex due to the subjective judgments required to forecast the expected royalty payments subject to the agreement and due to the nature and extent of audit effort required to address these matters. Specifically, as it related to pelecarsen, a product candidate that is not currently commercialized, these estimates include significant assumptions such as market penetration, probability of success, and sales price, among others, that are affected by expectations about future market conditions.

How We Addressed the Matter in Our Audit

We obtained an understanding, evaluated the design, and tested the operating effectiveness of controls over the Company's processes for estimating the amount and timing of future royalty payments.

To test the liability balance and the amount of interest expense recognized, our audit procedures included, among others, evaluating the methodology used and assessing the significant assumptions and the underlying data used by the Company in its effective interest model. We compared the significant assumptions in the estimate of future royalty payments to current industry and market trends. We recalculated the current year interest expense based on the amortization schedules and estimates of royalties using the effective interest method, and performed sensitivity analyses to evaluate the changes in the effective interest rate, and associated interest expense, that would result from changes in the assumptions.

/s/ Ernst & Young LLP

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

San Diego, California
February 21, 2024

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

	December 31, 2023	December 31, 2022
ASSETS		
Current assets:		
Cash and cash equivalents	$ 399,266	$ 276,472
Short-term investments	1,931,935	1,710,397
Contracts receivable	97,778	25,538
Inventories	28,425	22,033
Other current assets	184,449	168,254
Total current assets	2,641,853	2,202,694
Property, plant and equipment, net	71,043	74,294
Right-of-use assets	171,896	181,544
Deposits and other assets	105,280	75,344
Total assets	$ 2,990,072	$ 2,533,876
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 26,027	$ 17,921
Accrued compensation	67,727	49,178
Accrued liabilities	147,894	140,101
Income taxes payable	2,151	6,249
0.125 percent convertible senior notes, net	44,332	—
Current portion of deferred contract revenue	151,128	90,577
Other current liabilities	8,831	7,535
Total current liabilities	448,090	311,561
Long-term deferred contract revenue	241,184	287,768
1.75 percent convertible senior notes, net	562,285	—
0 percent convertible senior notes, net	625,380	622,242
0.125 percent convertible senior notes, net	—	544,504
Liability related to sale of future royalties, net	513,736	—
Long-term lease liabilities	170,875	178,941
Long-term obligations	41,836	15,973
Total liabilities	2,603,386	1,960,989
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 144,340,526 and 142,057,736 shares issued and outstanding at December 31, 2023 and December 31, 2022, respectively	144	142
Additional paid-in capital	2,215,098	2,059,850
Accumulated other comprehensive loss	(32,645)	(57,480)
Accumulated deficit	(1,795,911)	(1,429,625)
Total stockholders' equity	386,686	572,887
Total liabilities and stockholders' equity	$ 2,990,072	$ 2,533,876

See accompanying notes.

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

	Year Ended December 31,		
	2023	**2022**	**2021**
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 240,379	$ 242,314	$ 267,776
Other commercial revenue	68,212	61,044	74,619
Total commercial revenue	308,591	303,358	342,395
Research and development revenue:			
Collaborative agreement revenue	352,657	207,222	468,061
WAINUA joint development revenue	126,399	76,787	—
Total research and development revenue	479,056	284,009	468,061
Total revenue	787,647	587,367	810,456
Expenses:			
Cost of sales	9,133	14,116	10,842
Research, development and patent	899,625	833,147	643,453
Selling, general and administrative	232,619	150,295	186,347
Total operating expenses	1,141,377	997,558	840,642
Loss from operations	(353,730)	(410,191)	(30,186)
Other income (expense):			
Investment income	89,041	25,331	10,044
Interest expense	(12,660)	(8,122)	(9,349)
Interest expense related to sale of future royalties	(68,797)	—	—
Gain (loss) on investments	(1,914)	(7,333)	10,103
Gain (loss) on sale of real estate assets	(161)	149,604	—
Other income (expense)	14,256	(7,274)	(9,760)
Loss before income tax benefit (expense)	(333,965)	(257,985)	(29,148)
Income tax benefit (expense)	(32,321)	(11,737)	551
Net loss	$ (366,286)	$ (269,722)	$ (28,597)
Basic and diluted net loss per share	$ (2.56)	$ (1.90)	$ (0.20)
Shares used in computing basic and diluted net loss per share	143,190	141,848	141,021

See accompanying notes.

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

	Year Ended December 31,		
	2023	**2022**	**2021**
Net loss	$ (366,286)	$ (269,722)	$ (28,597)
Unrealized gains (losses) on investments, net of tax	24,484	(24,395)	(11,486)
Currency translation adjustment	351	(417)	(111)
Comprehensive loss	$ (341,451)	$ (294,534)	$ (40,194)

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(In thousands)

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity
Balance at December 31, 2020	140,366	$ 140	$ 1,895,519	$ (21,071)	$ (1,131,306)	$ 743,282
Net loss	—	—	—	—	(28,597)	(28,597)
Change in unrealized losses, net of tax	—	—	—	(11,486)	—	(11,486)
Foreign currency translation	—	—	—	(111)	—	(111)
Issuance of common stock in connection with employee stock plans	1,132	1	11,563	—	—	11,564
Issuance of warrants	—	—	89,752	—	—	89,752
Purchase of note hedges	—	—	(136,620)	—	—	(136,620)
Stock-based compensation expense	—	—	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)
Balance at December 31, 2021	141,210	$ 141	$ 1,964,167	$ (32,668)	$ (1,159,903)	$ 771,737
Net loss	—	—	—	—	(269,722)	(269,722)
Change in unrealized losses, net of tax	—	—	—	(24,395)	—	(24,395)
Foreign currency translation	—	—	—	(417)	—	(417)
Issuance of common stock in connection with employee stock plans	1,194	1	6,372	—	—	6,373
Stock-based compensation expense	—	—	100,264	—	—	100,264
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(346)	—	(10,953)	—	—	(10,953)
Balance at December 31, 2022	142,058	$ 142	$ 2,059,850	$ (57,480)	$ (1,429,625)	$ 572,887
Net loss	—	—	—	—	(366,286)	(366,286)
Change in unrealized gains, net of tax	—	—	—	24,484	—	24,484
Foreign currency translation	—	—	—	351	—	351
Issuance of common stock in connection with employee stock plans	2,283	2	49,439	—	—	49,441
Stock-based compensation expense	—	—	105,809	—	—	105,809
Balance at December 31, 2023	144,341	$ 144	$ 2,215,098	$ (32,645)	$ (1,795,911)	$ 386,686

See accompanying notes.

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

	Year Ended December 31,		
	2023	2022	2021
Operating activities:			
Net loss	$ (366,286)	$ (269,722)	$ (28,597)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	10,292	14,328	15,487
Amortization of right-of-use operating lease assets	9,647	5,362	1,721
Amortization of other assets	2,559	2,415	2,352
Amortization of premium (discount) on investments, net	(28,885)	7,389	17,776
Amortization of debt issuance costs	6,330	5,373	4,958
Non-cash royalty revenue related to sale of royalties	(44,628)	—	—
Non-cash interest related to sale of future royalties	68,238	—	—
Stock-based compensation expense	105,809	100,264	120,678
Loss (gain) on early retirement of debt	(13,389)	—	8,627
Non-cash losses related to disposal of property, plant and equipment	16,649	531	—
Loss (gain) on sale of real estate assets	161	(150,135)	—
Loss (gain) on investments	1,589	224	(1,092)
Non-cash losses related to other assets	1,661	2,030	2,707
Changes in operating assets and liabilities:			
Contracts receivable	(72,059)	36,358	14,308
Inventories	(6,392)	2,773	(2,841)
Other current and long-term assets	(29,840)	(24,682)	(877)
Accounts payable	8,119	1,094	(6,000)
Income taxes	(4,098)	6,213	(280)
Accrued compensation	18,549	10,368	(26,918)
Accrued liabilities and other current liabilities	(5,506)	46,695	(8,381)
Deferred contract revenue	13,967	(71,248)	(82,829)
Net cash provided by (used in) operating activities	(307,513)	(274,370)	30,799
Investing activities:			
Purchases of short-term investments	(1,770,814)	(1,485,772)	(1,124,193)
Proceeds from sale of short-term investments	1,584,676	989,152	1,344,185
Purchases of property, plant and equipment	(23,805)	(15,721)	(11,955)
Proceeds from sale of real estate assets	22	254,083	—
Acquisition of licenses and other assets, net	(4,206)	(4,378)	(5,946)
Purchases of strategic investments	—	—	(7,185)
Net cash provided by (used in) investing activities	(214,127)	(262,636)	194,906
Financing activities:			
Proceeds from equity, net	49,442	6,373	11,565
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	—	(10,953)	(16,725)
Proceeds from issuance of 1.75 percent convertible senior notes	575,000	—	—
1.75 percent convertible senior notes issuance costs	(14,175)	—	—
Repurchase of $504.4 million principal amount of 0.125 percent convertible senior notes	(487,943)	—	—
Proceeds from sale of future royalties	500,000	—	—
Payments of transaction costs related to sale of future royalties	(10,434)	(29)	—
Proceeds from real estate transaction	32,352	—	—
Proceeds from the issuance of 0 percent convertible senior notes	—	—	632,500
0 percent convertible senior notes issuance costs	—	—	(15,609)
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
Purchase of note hedges	—	—	(136,620)
Principal payments on debt	(160)	(50,686)	—
Net cash provided by (used in) financing activities	644,082	(55,295)	245,933
Effects of exchange rates on cash	352	(418)	(111)
Net increase (decrease) in cash and cash equivalents	122,794	(592,719)	471,527
Cash and cash equivalents at beginning of year	276,472	869,191	397,664
Cash and cash equivalents at end of year	$ 399,266	$ 276,472	$ 869,191
Supplemental disclosures of cash flow information:			
Interest paid	$ 6,512	$ 2,898	$ 4,778
Income taxes paid	$ 48,334	$ 5,010	$ 38
Supplemental disclosures of non-cash investing and financing activities:			
Right-of-use assets obtained in exchange for lease liabilities	$ —	$ 168,931	$ 6,641
Amounts accrued for capital and patent expenditures	$ 172	$ 4,767	$ 705

See accompanying notes.

IONIS PHARMACEUTICALS, INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

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 wholly owned subsidiary, Akcea Therapeutics, Inc. and its wholly owned subsidiaries ("we", "us" or "our").

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.

Use of Estimates

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States, or 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.

Revenue Recognition

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

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*, or ASC 808. ASC 808 does not address the recognition and measurement of collaborative arrangements and instead refers companies to use other authoritative accounting literature. 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 are within the scope of ASC 606, *Revenue from Contracts with Customers*. 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 WAINUA 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 selling, general and administrative, or SG&A, expense and research and development, or R&D, expense, respectively.

Steps to Recognize Revenue

For elements of our contractual relationships that we account for under ASC 606, we use a five-step process to determine the amount of revenue we should recognize and when we should recognize it. The five-step process is as follows:

1. *Identify the contract*

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

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

2. Identify the performance obligations

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

We may 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. When a partner exercises its option to license a medicine that was not previously determined to be a material right at the inception of the agreement or requests additional goods or services, then we identify a new performance obligation for that item.

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

3. Determine the transaction price

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

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable that 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.

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

For purposes of determining 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.

We recognize royalty revenue 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.

Under our distribution agreements with Swedish Orphan Biovitrum AB, or 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. We are also responsible for maintaining the marketing authorization for TEGSEDI and WAYLIVRA in major markets and 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. Under our agreements with Sobi, Sobi does not generally have a right of return.

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 sold 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-effect adjustment.

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.

Refer to Note 4, *Collaborative Arrangements and Licensing Agreements*, for further discussion of our 2018 Strategic Neurology collaboration with Biogen that included multiple agreements which we negotiated concurrently and in contemplation of one another.

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, 2023, approximately 87.8 percent of our contracts receivables were from one significant customer. As of December 31, 2022, approximately 82.5 percent of our contracts receivables were from one significant customer.

Unbilled SPINRAZA Royalties

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

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 in our consolidated balance sheets. During the years ended December 31, 2023 and 2022, we recognized $78.2 million and $73.5 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. For further discussion, refer to our revenue recognition policy above.

Cost of Sales

Our cost of sales is comprised of costs related to our commercial revenue, including 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.

Research, Development and Patent Expenses

Our research, development and patent expenses include wages, benefits, facilities, supplies, external services, clinical trial and manufacturing costs, patents and other expenses that are directly related to our R&D operations. We expense R&D costs as we incur them. When we make payments for R&D services prior to the services being rendered, we record those amounts as prepaid assets in our consolidated balance sheets and we expense them as the services are provided. A portion of the costs included in R&D expenses are costs associated with our partner agreements. In 2023, 2022 and 2021, patent expenses were $4.3 million, $4.7 million and $5.3 million, respectively.

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, we can provide no assurance that the final tax outcome of these matters will not be different from that which we have 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 we make such determination.

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.

Basic and Diluted Net Loss per Share

Basic net loss per share

We compute basic net loss per share by dividing our net loss by our weighted-average number of common shares outstanding during the period.

Diluted net loss per share

For the years ended December 31, 2023, 2022 and 2021, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock from the following would have had an anti-dilutive effect on net loss per share:

- 0 percent convertible senior notes, or 0% Notes;
- Note hedges related to the 0% Notes;
- 0.125 percent convertible senior notes, or 0.125% Notes;
- Note hedges related to the 0.125% 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, 2023, common stock underlying the 1.75 percent convertible senior notes, or 1.75% Notes, would also have had an anti-dilutive effect on net loss per share.

Additionally as of December 31, 2023, 2022 and 2021, we had warrants related to our 0% Notes and 0.125% 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.

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 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.

Stock Options and Stock Purchase Rights:

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. Historically, we estimated the expected term of options granted based on historical exercise patterns. In 2021, our Compensation Committee approved an amendment to the 2011 Equity Incentive Plan, or 2011 Plan, and the 2020 Equity Incentive Plan, or 2020 Plan, that increased the contractual term of stock options granted under these plans from seven years to ten years for stock options granted on January 1, 2022 and thereafter. We determined that we are unable to rely on our historical exercise data as a basis for estimating the expected life of stock options granted to employees following this change because the contractual term changed and we have no other means to reasonably estimate future exercise behavior. We therefore used the simplified method for determining the expected life of stock options granted to employees in the years ended December 31, 2023 and 2022. Under the simplified method, we calculate the expected term as the average of the time-to-vesting and the contractual life of the options. As we gain additional historical information, we will transition to calculating our expected term based on our historical exercise patterns.

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 we 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. Beginning in 2022, we added PRSU awards to the compensation for our other Section 16 officers. Under the terms of the PRSUs we granted in 2020 through 2022, 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. These PRSU awards also included an alternative three-year payout mechanism, or the Alternative Calculation, under which we must calculate an alternative payout at the end of the final three-year measurement period assuming the only measurement period for all shares under the award was the three-year period. If the Alternative Calculation is greater than payouts under the sum of the three years, then such PRSU award will pay out to achieve the number of shares payable under the Alternative Calculation.

Under the terms of the PRSUs we granted in 2023, 100 percent of the PRSUs may vest at the end of the three-year performance period based on our relative TSR as compared to a peer group of companies and as measured at the end of the 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 200 percent of the target number depending on our relative TSR.

We determined the fair value of the 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.

Refer to Note 8, *Stockholders' Equity,* for additional information regarding our stock-based compensation plans.

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.

Fair Value Measurements

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.

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 traded 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.

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 statements 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 public and private biotechnology companies that we received as part of a technology license or partner agreement. At December 31, 2023, we held equity investments in three publicly traded companies and seven privately held companies.

We are required to measure and record our equity investments at fair value and to recognize the changes in fair value in our consolidated statements of operations. We account for our equity investments in publicly traded companies at their listed stock price. 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.

Inventories

We reflect our inventory in our consolidated balance sheets 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.

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 we determine as the following (in years):

	Estimated Useful Lives
Computer software, laboratory, manufacturing and other equipment	3 to 10
Building, building improvements and building systems	15 to 40
Land improvements	20
Leasehold improvements	5 to 15
Furniture and fixtures	5 to 10

We depreciate our leasehold improvements using the shorter of the estimated useful life or remaining lease term. We evaluate long-lived assets, which include property, plant and equipment, 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.

Accrued Liabilities

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.

Convertible Debt

We 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. We record debt issuance costs as contra-liabilities in our consolidated balance sheets at issuance and amortize them over the contractual term of the convertible debt instrument using the effective interest rate. The balances of our convertible senior notes presented in our consolidated balance sheets represent the principal balance of each convertible debt instrument less debt issuance costs.

As of December 31, 2023, we had three outstanding convertible senior notes, our 1.75% Notes, which mature in June 2028, our 0% Notes, which mature in April 2026, and our 0.125% Notes, which mature in December 2024. Refer to Note 7, *Long-Term Obligations and Commitments*, for further details on our convertible senior notes.

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 sheets. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Liability Related to Sale of Future Royalties

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma Investments, or Royalty Pharma, to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our arrangements with Biogen and Novartis, respectively. Refer to Note 7, *Long-Term Obligations and Commitments*, for further details on the agreement.

Under our agreement with Royalty Pharma, we record upfront payments and milestone payments we receive from the sale of future royalties as a liability, net of transaction costs. We record royalty payments made to Royalty Pharma as a reduction of the liability or accrued interest and amortize the transaction costs over the estimated life of the royalty stream. We account for the associated interest expense under the effective interest rate method, while continuing to recognize the full amount of royalty revenue in the period in which the counterparty sells the related product and recognizes the related revenue.

We calculate the liability related to the sale of future royalties, effective interest rate and the related interest expense using our current estimate of anticipated future royalty payments under the arrangement, which we periodically reassess based on internal projections and information from our partners who are responsible for commercializing the medicines. If there is a material change in our estimate, we will prospectively adjust the effective interest rate and the related interest expense.

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 in our consolidated balance sheets 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 conclude we are reasonably certain to 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 use our incremental borrowing rate, based on the information available 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. Our leases do not include material variable or contingent lease payments. We recognize period expenses, such as common area maintenance expenses, in the period we incur the expense.

Segment Information

We operate 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.

Recently Issued Accounting Standards

In November 2023, the Financial Accounting Standards Board, or FASB, issued updated guidance on segment reporting. The guidance requires public companies with a single reportable segment to provide all disclosures required under ASC 280, *Segment Reporting*. In addition, the guidance requires public companies to include in interim reports all disclosures related to a reportable segment's profit or loss and assets that are currently required in annual reports. This update is effective for annual periods beginning after December 15, 2023 and interim periods beginning after December 15, 2024. The guidance is applied on a retrospective basis for all periods presented in the financial statements, unless it is impracticable. Early adoption of this guidance is permitted. We currently plan to adopt the annual reporting requirements in our 2024 Annual Report on Form 10-K. We plan to adopt the interim reporting requirements in our Quarterly Report on Form 10-Q in the first quarter of 2025.

In December 2023, the FASB issued updated guidance on income tax disclosures. The new guidance requires companies to provide additional disaggregation of information related to the income tax rate reconciliation and income tax payments. In addition, the guidance eliminates certain existing disclosure requirements related to uncertain tax positions and unrecognized deferred tax liabilities. This update is effective for annual periods beginning after December 15, 2024. Early adoption of this guidance is permitted. We currently plan to adopt this guidance in our 2025 Annual Report on Form 10-K.

We do not expect any other recently issued accounting standards to have a material impact to our financial results.

2. Supplemental Financial Data

Inventories

Our inventory consisted of the following (in thousands):

	December 31,	
	2023	2022
Raw materials:		
Raw materials- clinical	$ 20,985	$ 17,061
Raw materials- commercial	1,809	2,699
Total raw materials	22,794	19,760
Work in process	5,477	2,109
Finished goods	154	164
Total inventory	$ 28,425	$ 22,033

Property, Plant and Equipment

Our property, plant and equipment consisted of the following (in thousands):

	December 31,	
	2023	2022
Computer software, laboratory, manufacturing and other equipment	$ 79,885	$ 74,351
Building, building improvements and building systems	41,228	41,158
Leasehold improvements	28,276	28,357
Furniture and fixtures	9,844	9,575
	159,233	153,441
Less: Accumulated depreciation	(96,759)	(87,716)
	62,474	65,725
Land	8,569	8,569
Total	$ 71,043	$ 74,294

Accrued Liabilities

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

	December 31,	
	2023	2022
Clinical expenses	$ 105,967	$ 116,460
In-licensing expenses	7,454	7,945
Commercial expenses	4,875	3,498
Other miscellaneous expenses	29,598	12,198
Total accrued liabilities	$ 147,894	$ 140,101

3. Revenues

During the years ended December 31, 2023, 2022 and 2021, our revenues were comprised of the following (in thousands):

	Year Ended December 31,		
	2023	2022	2021
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 240,379	$ 242,314	$ 267,776
Other commercial revenue:			
TEGSEDI and WAYLIVRA revenue, net	34,913	30,051	55,500
Licensing and other royalty revenue	33,299	30,993	19,119
Total other commercial revenue	68,212	61,044	74,619
Total commercial revenue	308,591	303,358	342,395
Research and development revenue:			
Collaborative agreement revenue	352,657	207,222	468,061
WAINUA joint development revenue	126,399	76,787	—
Total research and development revenue	479,056	284,009	468,061
Total revenue	$ 787,647	$ 587,367	$ 810,456

Revenue Sources

The following are sources of revenue and when we typically recognize revenue.

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 earn royalty revenue on net sales of QALSODY which is included in Licensing and other royalty revenue.

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

We earn commercial revenue from TEGSEDI and WAYLIVRA sales under our distribution agreements with Sobi. In addition, we receive royalties from PTC Therapeutics International Limited, or PTC, for TEGSEDI and WAYLIVRA sales. Refer to Note 4, *Collaborative Arrangements and Licensing Agreements*, for details on our commercialization partnerships with Sobi and PTC.

Research and development revenue under collaboration agreements

We 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, R&D services and manufacturing services.

Upfront payments: When we enter into a collaboration agreement and receive 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.

Milestone payments: We include variable 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, when we achieve a milestone payment from a partner for advancing a clinical study under a collaboration agreement, we add the milestone payment to the transaction price if the milestone relates to an ongoing R&D services performance obligation and recognize revenue related to the milestone payment over our estimated period of performance. If we have partially completed our performance obligation, then we record a cumulative-effect adjustment in the period we add the milestone payment to the transaction price.

Conversely, we recognize in full those milestone payments that we earn based on our partners' activities when our partner achieves the milestone event and we do not have a performance obligation.

License fees: We 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 who has full use of the license and we do not have any additional performance obligations related to the license after delivery.

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.

WAINUA (Eplontersen) Collaboration with AstraZeneca

In December 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize WAINUA for the treatment of transthyretin amyloidosis, or ATTR. We jointly developed and are preparing to commercialize WAINUA with AstraZeneca in the U.S. We initially granted AstraZeneca exclusive rights to commercialize WAINUA outside the U.S., except for certain Latin American countries. In July 2023, we expanded those rights to include Latin America. Under the terms of the agreement, we received a $200 million upfront payment in 2021.

We evaluated our WAINUA 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 are performing, (iii) the co-commercialization activities that we and AstraZeneca are performing and (iv) the co-medical affairs activities that we and AstraZeneca are performing.

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 and therefore do not have a vendor-customer relationship. AstraZeneca is currently responsible for 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading the Phase 3 development program, we made an accounting policy election to recognize as non-customer revenue the cost-share funding from AstraZeneca, net of our share of AstraZeneca's development expenses, 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 WAINUA to market outside the U.S., we made an accounting policy election to recognize cost-share funding we receive from AstraZeneca related to commercial and medical affairs activities as reductions of our SG&A expense and R&D expense, respectively.

4. 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. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. Under our 2013 strategic neurology collaboration, Biogen developed QALSODY (tofersen), our medicine that received accelerated approval in the U.S. to treat patients with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS. In addition, we and Biogen are currently developing numerous other investigational medicines to treat neurodegenerative diseases, including medicines in development to treat people with amyotrophic lateral sclerosis, or ALS, SMA, Angelman Syndrome, or AS, Alzheimer's disease, or AD, and Parkinson's disease, or PD. 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 31, 2023, we have received nearly $3.8 billion from our Biogen collaborations, including payments to purchase our stock.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA. From inception through December 31, 2023, we earned more than $2.1 billion in total revenue under our SPINRAZA collaboration, including more than $1.6 billion in revenue from SPINRAZA royalties and more than $425 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.

In 2023, we entered into a royalty purchase agreement with Royalty Pharma in which Royalty Pharma receives 25 percent of our SPINRAZA royalty payments from 2023 through 2027, increasing to 45 percent of royalty payments in 2028, on up to $1.5 billion in annual sales. Royalty Pharma's royalty interest in SPINRAZA will revert to us after total SPINRAZA royalty payments to Royalty Pharma reach either $475 million or $550 million, depending on the timing and occurrence of the U.S. Food and Drug Administration, or FDA, approval of pelacarsen, which Novartis is developing. Refer to Note 7, *Long-Term Obligations and Commitments*, for further discussion of this agreement.

New Antisense Medicines for the Treatment of SMA

In 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.

At the commencement of this collaboration, we received a $25 million upfront payment from Biogen. In 2021, Biogen exercised its option to license ION306, a drug we discovered under this collaboration, for which we earned a $60 million license fee payment. We recognized this payment as revenue in full because Biogen had full use of the license without any continuing involvement from us. 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. We will receive development and regulatory milestone payments from Biogen if new medicines, including ION306, advance towards marketing approval.

Over the term of the collaboration, we are eligible to receive up to $555 million if Biogen advances ION306, which is comprised of up to $45 million in development milestone payments, up to $110 million in regulatory milestone payments and up to $400 million in sales milestone payments. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration. From inception through December 31, 2023, we received $85 million in payments under this collaboration. We will achieve the next payment of up to $45 million for the initiation of a Phase 3 trial under this collaboration.

Neurology Collaborations

2018 Strategic Neurology

In 2018, we and Biogen entered into a strategic collaboration to develop novel antisense medicines for a broad range of neurological diseases. We also 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. In most cases, Biogen will be responsible for conducting IND-enabling toxicology studies for the selected medicine. Biogen has 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.

At the commencement of this collaboration, 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.

For each medicine under this collaboration, we are eligible to receive up to $270 million, which is comprised of a $15 million license fee, up to $105 million in development milestone payments and up to $150 million in regulatory milestone payments. 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 multiple programs under this collaboration. From inception through December 31, 2023, we have received nearly $1.1 billion in payments under this collaboration, including payments to purchase our stock. We will achieve the next payment of up to $15 million if Biogen licenses a medicineunder this collaboration.

We considered that the collaboration agreement and SPA 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. 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 31, 2023, we have included $623 million in upfront and milestone payments in the transaction price for our R&D services performance obligation under this collaboration, including a $7.5 million milestone payment we achieved in the fourth quarter of 2023. This milestone payment did not create a new performance obligation because it is part of our original R&D services performance obligation. Therefore, we included this amount 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 2013, we and Biogen entered into a 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. In most cases, we are 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 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 four investigational medicines in development under this collaboration, including a medicine for Parkinson's disease (ION859), two medicines for ALS (QALSODY and ION541) and a medicine for multiple system atrophy (ION464). In 2018, Biogen exercised its option to license QALSODY, our medicine that received accelerated approval in April 2023 from the FDA for the treatment of adult patients with SOD1-ALS. As a result, Biogen is responsible for global development, regulatory and commercialization activities and costs for QALSODY.

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.

Over the term of the collaboration for QALSODY, we are eligible to receive nearly $110 million, which is comprised of a $35 million license fee we received when Biogen licensed QALSODY from us in 2018, $18 million in development milestone payments and up to $55 million in regulatory milestone payments. In addition, we are eligible to receive tiered royalties ranging from 11 percent to 15 percent on net sales of QALSODY. We will achieve the next milestone payment for QALSODY of $20 million if the European Medicines Agency, or EMA, approves Biogen's Marketing Authorization Application, or MAA, filing of QALSODY.

For each of the other antisense molecules that are chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million, which is comprised of a $70 million license fee, up to $60 million in development milestone payments and up to $130 million in regulatory 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. From inception through December 31, 2023, we have received more than $325 million in payments under our 2013 strategic neurology collaboration. We will achieve the next payment of $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. During 2020, we completed our remaining R&D 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 period we generated the payment because we did not have any performance obligations for the respective payment. For example, in 2023, we earned a $16 million milestone payment from Biogen when the FDA approved Biogen's New Drug Application, or NDA, for QALSODY, which we recognized in full because we did not have any remaining performance obligations related to this milestone payment.

2012 Neurology

In 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, Biogen is conducting the IONIS-MAPT$_{Rx}$ study for AD and we are currently advancing 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 2019, Biogen exercised its option to license IONIS-MAPT$_{Rx}$ and as a result Biogen is 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. For each program under this collaboration, we are eligible to receive up to $210 million, which is comprised of a license fee of up to $70 million, up to $10 million in development milestone payments and up to $130 million in regulatory milestone payments, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales of any medicines resulting from each of the two programs. From inception through December 31, 2023, we have received more than $230 million in payments under this collaboration, including $39 million in milestone payments we received from Biogen for advancing ION582 during 2023 and a $10 million milestone payment we received from Biogen when Biogen advanced IONIS-MAPT$_{Rx}$ during 2022. We will achieve the next payment of $70 million if Biogen licenses ION582 under this collaboration.

When we commenced development for IONIS-MAPT$_{Rx}$ and ION582, we identified two separate performance obligations as our development work for each medicine. 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 obligations. In 2022, we completed our R&D services performance obligation for IONIS-MAPT$_{Rx}$. From inception through December 31, 2023, we have included $57 million in the transaction price for our IONIS-MAPT$_{Rx}$ development performance obligation, including $19.5 million of milestone payments we earned from Biogen in 2020 when we advanced IONIS-MAPT$_{Rx}$. From inception through December 31, 2023, we have included $68 million in milestone payments in the transaction price for our ION582 development performance obligation, including $39 million in milestone payments we received from Biogen for advancing ION582 during 2023.

During the years ended December 31, 2023, 2022 and 2021, we earned the following revenue from our relationship with Biogen (in thousands, except percentage amounts):

	Year Ended December 31,		
	2023	**2022**	**2021**
Revenue from our relationship with Biogen	$ 350,146	$ 366,696	$ 428,784
Percentage of total revenue	44%	62%	53%

Our consolidated balance sheets at December 31, 2023 and 2022 included deferred revenue of $307.4 million and $351.2 million, respectively, related to our relationship with Biogen.

Joint Development and Commercialization Arrangement

AstraZeneca

WAINUA (Eplontersen) Collaboration

In 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. In December 2023, the FDA approved eplontersen with the brand name, WAINUA, in the U.S. for ATTRv-PN. We are jointly developing and commercializing WAINUA with AstraZeneca in the U.S. We initially granted AstraZeneca exclusive rights to commercialize WAINUA outside the U.S., except for certain Latin American countries. In July 2023, we expanded those rights to include Latin America.

Over the term of the collaboration, we are eligible to receive up to $3.6 billion, which is comprised of a $200 million upfront payment, a $20 million license fee, up to $485 million in development and approval milestone payments and up to $2.9 billion in sales milestone payments. The agreement 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 ranging from mid to high teens for sales outside the U.S. From inception through December 31, 2023, we have received nearly $360 million in payments under this collaboration. We will achieve the next payment of $30 million upon regulatory approval of WAINUA for ATTRv-PN in the EU under this collaboration.

We evaluated our WAINUA 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 in 2021. In 2023, we earned a $20 million license fee payment when we licensed rights to Latin America for WAINUA to AstraZeneca. We recognized these payments in full because we did not have any remaining performance obligations after we delivered the licenses 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 is currently responsible for 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading the Phase 3 development program, we 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 WAINUA to market outside the U.S., we recognize cost-share funding we receive from AstraZeneca related to these activities as a reduction of our commercial and medical affairs expenses. In 2023, we earned a $50 million milestone payment when the FDA approved WAINUA for ATTRv-PN in the U.S. We recognized this milestone payment in full as joint development revenue because we did not have any remaining performance obligations related to the milestone payment.

Research and Development Partners

AstraZeneca

In addition to our collaboration for WAINUA, we have a collaboration with AstraZeneca focused on discovering and developing treatments for cardiovascular, renal and metabolic diseases, which we formed in 2015. Under our collaboration, AstraZeneca has licensed multiple 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.

Over the term of the collaboration, we are eligible to receive up to $3.4 billion, which is comprised of a $65 million upfront payment, up to $290 million in license fees, up to $865 million in development milestone payments and up to $2.2 billion in regulatory milestone payments. 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 31, 2023, we have received more than $300 million in payments under this collaboration. We will achieve the next payment of $10 million if AstraZeneca advances a medicine under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for AstraZeneca. We determined the transaction price to be the $65 million upfront payment we received and we allocated it to our single performance obligation. We 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 2021. 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. From inception through the completion of our performance obligation, 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 period we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. For example, in 2023, we earned a $36 million payment when AstraZeneca licensed ION826 from us. We recognized this payment in full in 2023 because we did not have any remaining performance obligations after we delivered the license to AstraZeneca.

During the years ended December 31, 2023, 2022 and 2021, we earned the following revenue from our relationship with AstraZeneca (in thousands, except percentage amounts):

	Year Ended December 31,		
	2023	2022	2021
Revenue from our relationship with AstraZeneca	$ 202,236	$ 79,160	$ 254,591
Percentage of total revenue	26%	13%	31%

We did not have any deferred revenue from our relationship with AstraZeneca at December 31, 2023 and 2022.

GSK

In 2010, we entered into a collaboration with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for serious and rare diseases, including infectious diseases. Upon initiating the collaboration, we received an upfront payment of $35 million. Under our collaboration, GSK is developing bepirovirsen for the treatment of chronic hepatitis B virus infection, or 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.

Over the term of the collaboration, we are eligible to receive nearly $260 million, which is comprised of a $25 million license fee, up to $42.5 million in development milestone payments, up to $120 million in regulatory milestone payments and up to $70 million in sales milestone payments if GSK successfully develops and commercializes bepirovirsen. In addition, we are eligible to receive tiered royalties up to the low-teens on net sales of bepirovirsen. From inception through December 31, 2023, we have received more than $105 million in an upfront payment and payments related to the HBV program.

We completed our R&D services performance obligations in 2015, therefore 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. In 2023, we earned a $ million milestone payment when GSK initiated a Phase 3 program of bepirovirsen. We recognized this milestone payment as R&D revenue in full in 2023 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of $15 million if the FDA accepts an NDA filing of bepirovirsen for review.

During the years ended December 31, 2023, 2022 and 2021, we earned the following revenue from our relationship with GSK (in thousands, except percentage amounts):

	Year Ended December 31,		
	2023	2022	2021
Revenue from our relationship with GSK	$ 15,000	$ —	$ —
Percentage of total revenue	2%	0%	0%

We did not have any deferred revenue from our relationship with GSK at December 31, 2023 and 2022.

Novartis

Pelacarsen Collaboration

In 2017, we initiated a collaboration with Novartis to develop and commercialize pelacarsen. Novartis is responsible for conducting and funding development and regulatory activities for pelacarsen, including a global Phase 3 cardiovascular outcomes study that Novartis initiated in 2019.

Over the term of the collaboration, we are eligible to receive up to $900 million, which is comprised of a $75 million upfront payment, a $150 million license fee, a $25 million development milestone payment, up to $290 million in regulatory milestone payments and up to $360 million in sales milestone payments. We are also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of pelacarsen. From inception through December 31, 2023, we have received more than $275 million in payments under this collaboration. We will achieve the next payment of $50 million if the FDA accepts an NDA filing 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 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 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.

As described in the *Biogen SPINRAZA* section above, in January 2023, we entered into a royalty purchase agreement with Royalty Pharma. Under the agreement, in addition to a minority interest in SPINRAZA royalties, Royalty Pharma will receive 25 percent of any future royalty payments on pelacarsen. Refer to Note 7, *Long-Term Obligations and Commitments*, for further discussion of this agreement.

New Medicine for the Treatment of Lp(a)-Driven Cardiovascular Disease

In August 2023, we entered into a collaboration and license agreement with Novartis for the discovery, development and commercialization of a novel medicine for patients with Lp(a)-driven cardiovascular disease, or CVD. Novartis is solely responsible for the development, manufacturing and potential commercialization of the next generation Lp(a) therapy.

Over the term of the collaboration, we are eligible to receive up to $730 million, which is comprised of a $60 million upfront payment, up to $155 million in development milestone payments, up to $105 million in regulatory milestone payments and up to $410 million in sales milestone payments. In addition, we are eligible to receive tiered royalties ranging from 10 percent to 20 percent on net sales. From inception through December 31, 2023, we have received $60 million from the upfront payment we received under this collaboration. We will achieve the next payment of $5 million if we designate a development candidate under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Novartis. We determined the transaction price to be the $60 million upfront payment we received in the fourth quarter 2023. We allocated the transaction price to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation at the end of the research term in June 2024.

During the years ended December 31, 2023, 2022 and 2021, we earned the following revenue from our relationship with Novartis (in thousands, except percentage amounts):

	Year Ended December 31,		
	2023	2022	2021
Revenue from our relationship with Novartis	$ 30,194	$ 237	$ 25,526
Percentage of total revenue	4%	Less than 1%	3%

Our consolidated balance sheet at December 31, 2023 included deferred revenue of $30.0 million related to our relationship with Novartis. We did not have any deferred revenue from our relationship with Novartis at December 31, 2022.

Roche

Huntington's Disease

In 2013, we entered into an agreement with Hoffmann-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 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen. As a result, Roche is responsible for all global development, regulatory and commercialization activities and costs for tominersen.

Over the term of the collaboration, we are eligible to receive up to $395 million, which is comprised of a $30 million upfront payment, a $45 million license fee, up to $70 million in development milestone payments, up to $170 million in regulatory milestone payments and up to $80 million in sales 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 of any product resulting from this collaboration. From inception through December 31, 2023, we have received more than $150 million in payments under this collaboration. We will achieve the next payment of $17.5 million if Roche advances a medicine under this collaboration.

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 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 period in which we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. In 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 independent data monitoring committee, or iDMC.

In January 2023, Roche initiated the Phase 2, GENERATION HD2, study of tominersen in patients with prodromal or early manifest HD. Roche is focusing on early-stage and younger patients based on the post-hoc analyses from the GENERATION HD1 study that suggested tominersen may benefit these patient groups. 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 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 multiple studies in two disease indications for IONIS-FB-L_{Rx}, one for the treatment of patients with immunoglobulin A, or IgA, nephropathy, or IgAN, and one for the treatment of patients with GA, the advanced stage of dry AMD. In April 2023, Roche initiated a Phase 3 study of IONIS-FB-L_{Rx} in patients with IgAN.

After positive data from a Phase 2 clinical study in patients with IgAN, Roche licensed IONIS-FB-L_{Rx} in 2022 for $35 million. As a result, Roche is responsible for global development, regulatory and commercialization activities, and costs for IONIS-FB-L_{Rx}, except for the open label Phase 2 study in patients with IgAN and the Phase 2 study in patients with GA, both of which we are conducting and funding. In 2022, we amended our IONIS-FB-L_{Rx} collaboration agreement with Roche. The amendment changed future potential milestone payments we could receive under the collaboration. We determined there were no changes that would require adjustments to revenue we previously recognized.

Over the term of the collaboration, we are eligible to receive more than $810 million, which is comprised of a $75 million upfront payment, a $35 million license fee, up to $145 million in development milestone payments, up to $279 million in regulatory milestone payments and up to $280 million in sales milestone payments. In addition, we are also eligible to receive tiered royalties from the high teens to 20 percent on net sales. From inception through December 31, 2023, we have received more than $135 million in payments under this collaboration. We will achieve the next payment of up to $90 million if Roche advances IONIS-FB-L_{Rx} under this collaboration.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Roche. From inception through December 31, 2023, we have included $97 million in upfront and milestone payments in the transaction price for our R&D services performance obligation under this collaboration, including $22 million of milestone payments we achieved in 2022. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in the fourth quarter of 2024.

RNA-Targeting Medicines for Alzheimer's Disease and Huntington's Disease

In September 2023, we entered into an agreement with Roche to develop two undisclosed early-stage programs for RNA-targeting investigational medicines for the treatment of AD and HD. Under the agreement, we are responsible for advancing the two programs through preclinical studies and Roche is responsible for clinical development, manufacturing and commercialization of the medicines if they receive regulatory approval.

Over the term of the collaboration, we are eligible to receive up to $625 million, which is comprised of a $60 million upfront payment, up to $167 million in development milestone payments and up to $398 million in sales milestone payments. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales. From inception through December 31, 2023, we have received $60 million from the upfront payment we received under this collaboration. We will achieve the next payment of $7.5 million if we advance a medicine under this collaboration.

We identified two performance obligations under this new agreement, comprised of R&D services for each of the two separate programs. We determined the transaction price to be the $60 million upfront payment we received in the fourth quarter 2023. We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $45 million for the R&D services for the investigational medicine for AD; and
- $15 million for the R&D services for the investigational medicine for HD.

We are recognizing revenue for our R&D services performance obligations as we perform services based on our effort to satisfy our performance obligations relative to our total effort expected to satisfy our performance obligations. We currently estimate we will satisfy our performance obligations at the end of the research terms of March 2024 and March 2025 for the investigational medicines for AD and HD, respectively.

During the years ended December 31, 2023, 2022 and 2021, we earned the following revenue from our relationship with Roche (in thousands, except percentage amounts):

	Year Ended December 31,		
	2023	**2022**	**2021**
Revenue from our relationship with Roche	$ 48,838	$ 67,202	$ 17,241
Percentage of total revenue	6%	11%	2%

Our consolidated balance sheets at December 31, 2023 and 2022 included deferred revenue of $36.7 million and $22.4 million related to our relationship with Roche, respectively.

Commercialization Partnerships

Otsuka

In December 2023, we entered into an agreement with Otsuka Pharmaceutical Co., Ltd., or Otsuka, to commercialize donidalorsen in Europe. We are responsible for the ongoing development of donidalorsen. We retained the rights to commercialize donidalorsen in the U.S. and in the rest of the world assuming regulatory approval.

Over the term of the collaboration, we are eligible to receive up to $185 million, which is comprised of a $65 million upfront payment, up to $50 million in regulatory milestone payments and up to $70 million in sales milestone payments. In addition, we are eligible to receive tiered royalties ranging from 20 percent to 30 percent on net sales. From inception through December 31, 2023, we have received $65 million from the upfront payment we received under this collaboration. We will achieve the next payment of $15 million if the EMA accepts a MAA filing for donidalorsen in the EU under this collaboration.

We identified two performance obligations under this new agreement, comprised of our license of donidalorsen to Otsuka and R&D services for donidalorsen. We determined the transaction price to be the $65 million upfront payment we received in the fourth quarter 2023. We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $56 million for the license of donidalorsen; and
- $9 million for the R&D services for donidalorsen.

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 obligations in March 2026.

During the year ended December 31, 2023, we earned the following revenue from our relationship with Otsuka (in thousands, except percentage amount):

	Year Ended December 31, 2023
Revenue from our relationship with Otsuka	$ 56,480
Percentage of total revenue	7%

Our consolidated balance sheets at December 31, 2023 included deferred revenue of $8.5 million related to our relationship with Otsuka.

PTC Therapeutics

In 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 and September 2023, we started receiving royalties from PTC for TEGSEDI and WAYLIVRA sales, respectively.

Swedish Orphan Biovitrum AB (Sobi)

In 2021, we began commercializing TEGSEDI and WAYLIVRA in Europe and TEGSEDI in North America through distribution agreements with Sobi. Under our distribution agreements, Sobi is responsible for commercializing TEGSEDI and WAYLIVRA in Europe and TEGSEDI in North America, respectively. We are responsible for supplying finished goods inventory to Sobi and Sobi is responsible for selling each medicine to the end customer. Under our agreements with Sobi, Sobi does not generally have a right of return. We recognize as revenue the price Sobi pays us for the inventory when we deliver the finished goods inventory to Sobi. In addition, we earn a distribution fee on net sales from Sobi for each medicine.

In October 2023, our distribution agreement for TEGSEDI in North America was terminated. As a result, we are currently transitioning responsibilities from Sobi to us in order to continue serving the impacted patient community. In February 2024, we began the process to withdraw the TEGSEDI NDA.

During the years ended December 31, 2023, 2022 and 2021, we earned the following revenue from our distribution agreement with Sobi for TEGSEDI in North America (in thousands, except percentage amounts):

	Year Ended December 31,		
	2023	2022	2021
TEGSEDI revenue from our distribution agreement with Sobi in North America	$ 2,646	$ 4,004	$ 7,443
Percentage of total revenue	Less than 1%	1%	1%

Technology Enhancement Collaborations

Bicycle Therapeutics

In 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 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 restricted 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.

Metagenomi

In 2022, we entered into a collaboration and license agreement with Metagenomi to research, develop and commercialize investigational medicines for up to four initial genetic targets, and, upon the achievement of certain development milestones, four additional genetic targets using gene editing technologies. As a result, we paid $80 million to license Metagenomi's technologies and will pay Metagenomi certain fees for the selection of genetic targets. We recorded the $80 million payment as R&D expense in 2022 upon receiving a license from Metagenomi for intellectual property that is in research with no current alternate use. In addition, we will pay Metagenomi milestone payments and royalties that are contingent on the achievement of certain development, regulatory and sales events. We will also reimburse Metagenomi for certain of its costs in conducting its research and drug discovery activities under the collaboration.

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.

During the years ended December 31, 2023, 2022 and 2021, we earned the following revenue from our relationship with Alnylam (in thousands, except percentage amounts):

	Year Ended December 31,		
	2023	2022	2021
Revenue from our relationship with Alnylam	$ 28,426	$ 21,389	$ —
Percentage of total revenue	4%	4%	0%

We did not have any deferred revenue from our relationship with Alnylam at December 31, 2023 and 2022.

5. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2023:

One year or less	68%
After one year but within two years	24%
After two years but within three and a half years	8%
Total	100%

As illustrated above, at December 31, 2023, 92 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.

We invest in debt securities with strong credit ratings and an investment grade rating at or above A-1, P-1 or F-1 by Standard & Poor's, Moody's or Fitch, respectively.

At December 31, 2023, we had an ownership interest of less than 20 percent in seven private companies and three public companies with which we conduct business.

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

December 31, 2023	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (1)	$ 559,967	$ 157	$ (2,625)	$ 557,499
Debt securities issued by U.S. government agencies	224,711	64	(611)	224,164
Debt securities issued by the U.S. Treasury (1)	513,784	152	(1,889)	512,047
Debt securities issued by states of the U.S. and political subdivisions of the states	17,757	42	(113)	17,686
Total securities with a maturity of one year or less	1,316,219	415	(5,238)	1,311,396
Corporate debt securities	243,151	1,270	(692)	243,729
Debt securities issued by U.S. government agencies	110,138	547	(21)	110,664
Debt securities issued by the U.S. Treasury	294,873	1,239	(480)	295,632
Debt securities issued by states of the U.S. and political subdivisions of the states	3,466	7	(4)	3,469
Total securities with a maturity of more than one year	651,628	3,063	(1,197)	653,494
Total available-for-sale securities	$ 1,967,847	$ 3,478	$ (6,435)	$ 1,964,890
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ 236	$ (5,832)	$ 6,301
Privately held securities included in deposits and other assets (3)	23,115	25,001	(5,125)	42,991
Total equity securities	$ 35,012	$ 25,237	$ (10,957)	$ 49,292
Total available-for-sale and equity securities	$ 2,002,859	$ 28,715	$ (17,392)	$ 2,014,182

December 31, 2022	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Available-for-sale securities:				
Corporate debt securities (1)	$ 513,790	$ 23	$ (4,365)	$ 509,448
Debt securities issued by U.S. government agencies	133,585	—	(1,829)	131,756
Debt securities issued by the U.S. Treasury (1)	512,655	23	(5,124)	507,554
Debt securities issued by states of the U.S. and political subdivisions of the states	57,484	18	(686)	56,816
Other municipal debt securities	6,008	—	(14)	5,994
Total securities with a maturity of one year or less	1,223,522	64	(12,018)	1,211,568
Corporate debt securities	227,631	14	(10,143)	217,502
Debt securities issued by U.S. government agencies	34,339	—	(1,040)	33,299
Debt securities issued by the U.S. Treasury	245,030	—	(4,109)	240,921
Debt securities issued by states of the U.S. and political subdivisions of the states	18,314	116	(329)	18,101
Total securities with a maturity of more than one year	525,314	130	(15,621)	509,823
Total available-for-sale securities	$ 1,748,836	$ 194	$ (27,639)	$ 1,721,391
Equity securities:				
Publicly traded equity securities included in other current assets (2)	$ 11,897	$ —	$ (1,358)	$ 10,539
Privately held equity securities included in deposits and other assets (3)	23,115	17,257	—	40,372
Total equity securities	$ 35,012	$ 17,257	$ (1,358)	$ 50,911
Total available-for-sale and equity securities	$ 1,783,848	$ 17,451	$ (28,997)	$ 1,772,302

(1) Includes investments classified as cash equivalents in our consolidated balance sheets.

(2) Our publicly traded equity securities are included in other current assets. We recognize publicly traded equity securities at fair value. In the year ended December 31, 2023, we recorded a $4.2 million net unrealized loss in our consolidated statements of operations related to changes in the fair value of our investments in publicly traded companies.

(3) Our privately held equity securities are included in deposits and other assets. We recognize our privately held 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, which are Level 3 inputs. In the year ended December 31, 2023, we recorded a $2.6 million net unrealized gain in our consolidated statements of operations related to changes in the fair value of our investments in privately held companies.

The following is a summary of our investments we considered to be temporarily impaired at December 31, 2023 (in thousands, except for number of investments):

		Less than 12 Months of Temporary Impairment		More than 12 Months of Temporary Impairment		Total Temporary Impairment	
	Number of Investments	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
Corporate debt securities	297	$ 323,708	$ (553)	$ 178,183	$ (2,764)	$ 501,891	$ (3,317)
Debt securities issued by U.S. government agencies	63	199,372	(246)	14,777	(386)	214,149	(632)
Debt securities issued by the U.S. Treasury	34	325,966	(1,031)	131,000	(1,338)	456,966	(2,369)
Debt securities issued by states of the U.S. and political subdivisions of the states	61	8,352	(17)	7,888	(100)	16,240	(117)
Total temporarily impaired securities	455	$ 857,398	$ (1,847)	$ 331,848	$ (4,588)	$ 1,189,246	$ (6,435)

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 rather than underlying credit deterioration for any of the issuers. We believe it is more likely than not that we will be able to hold our debt securities with declines in value to maturity. Therefore, we intend to hold these securities to maturity and anticipate full recovery of our debt securities' amortized cost basis at maturity.

6. Fair Value Measurements

The following tables present the major security types we held at December 31, 2023 and 2022 that we regularly measure and carry at fair value. 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, 2023	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 185,424	$ 185,424	$ —
Corporate debt securities (2)	801,228	—	801,228
Debt securities issued by U.S. government agencies (3)	334,828	—	334,828
Debt securities issued by the U.S. Treasury (3)	807,679	807,679	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	21,155	—	21,155
Publicly traded equity securities included in other current assets (5)	6,301	6,301	—
Total	$ 2,156,615	$ 999,404	$ 1,157,211

	At December 31, 2022	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 211,655	$ 211,655	$ —
Corporate debt securities (4)	726,950	—	726,950
Debt securities issued by U.S. government agencies (3)	165,055	—	165,055
Debt securities issued by the U.S. Treasury (3)	748,475	748,475	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	74,917	—	74,917
Other municipal debt securities (3)	5,994	—	5,994
Publicly traded equity securities included in other current assets (5)	10,539	10,539	—
Total	$ 1,943,585	$ 970,669	$ 972,916

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

(2) $33.0 million was included in cash and cash equivalents, with the difference included in short-term investments in our consolidated balance sheets.

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

(4) $11.0 million was included in cash and cash equivalents, with the difference included in short-term investments in our consolidated balance sheets.

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

Convertible Notes

Our 1.75% Notes, 0% Notes and 0.125% Notes had a fair value of $661.1 million, $667.8 million and $42.4 million at December 31, 2023, 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.

7. Long-Term Obligations and Commitments

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

	December 31,	
	2023	2022
1.75% convertible senior notes	$ 562,285	$ —
0% convertible senior notes	625,380	622,242
0.125% convertible senior notes	—	544,504
Liability related to sale of future royalties	513,736	—
Lease liabilities	178,969	186,156
Mortgage debt	8,859	8,998
Other obligations	33,714	7,295
Total	$ 1,922,943	$ 1,369,195
Less: current portion	(8,831)	(7,535)
Total Long-Term Obligations	$ 1,914,112	$ 1,361,660

As of December 31, 2023, our 0.125% Notes was classified as a current liability because it matures in December 2024.

Convertible Debt and Call Spread

1.75% Convertible Senior Notes

In 2023, we completed a $575.0 million offering of convertible senior notes and used $488.2 million of the net proceeds from the issuance of the 1.75% Notes to repurchase $504.4 million in principal of our 0.125% Notes. We expect to use the remaining net proceeds to settle the 0.125% Notes that remain outstanding.

At December 31, 2023, we had the following 1.75% Notes outstanding (in millions, except interest rate and price per share data):

	1.75% Notes
Outstanding principal balance	$ 575.0
Unamortized debt issuance costs	$ 12.7
Maturity date	June 2028
Interest rate	1.75%
Effective interest rate	2.3%
Conversion price per share	$ 53.73
Total shares of common stock subject to conversion	10.7

0% Convertible Senior Notes and Call Spread

In 2021, we completed a $632.5 million offering of convertible senior notes. We used $319.0 million of the net proceeds from the issuance of the 0% Notes to pay the remaining $309.9 million principal balance of our 1% Notes in 2021.

At December 31, 2023, we had the following 0% Notes outstanding (in millions, except interest rate and price per share data):

	0% Notes
Outstanding principal balance	$ 632.5
Unamortized debt issuance costs	$ 7.2
Maturity date	April 2026
Interest rate	0%
Effective interest rate	0.5%
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 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 sheets. Refer to Note 1, *Organization and Significant Accounting Policies*, for our Call Spread accounting policy. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

0.125% Convertible Senior Notes and Call Spread

In 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our 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.

As discussed above, in 2023, we repurchased $504.4 million of our 0.125% Notes. We are holding the repurchased 0.125% Notes in treasury until maturity. As a result, the remaining principal balance of our 0.125% Notes was $44.5 million as of December 31, 2023. Additionally, during the year ended December 31, 2023, we recorded a $13.4 million gain on the early retirement of debt, which we recorded as other income in our consolidated statements of operations. The gain on the early retirement of our debt is the difference between the amounts paid to repurchase our 0.125% Notes and the net carrying balance of the liability at the time that we completed the repurchases.

At December 31, 2023, we had the following 0.125% Notes outstanding with interest payable semi-annually (in millions, except interest rate and price per share data):

	0.125% Notes
Outstanding principal balance	$ 44.5
Unamortized debt issuance costs	$ 0.2
Maturity date	December 2024
Interest rate	0.125%
Effective interest rate	0.5%
Conversion price per share	$ 83.28
Effective conversion price per share with call spread	$ 123.38
Total shares of common stock subject to conversion, excluding shares related to 0.125% Notes we have repurchased and are currently holding in treasury	0.5

In conjunction with the issuance of our 0.125% Notes in 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 sheets. Refer to Note 1, *Organization and Significant Accounting Policies*, for our Call Spread accounting policy. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Other Terms of Convertible Senior Notes

The 1.75%, 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.

Our total interest expense for our outstanding senior convertible notes for the years ended December 31, 2023, 2022 and 2021 included $5.9 million, $5.3 million and $4.9 million, respectively, of non-cash interest expense related to the amortization of debt issuance costs for our convertible notes.

Financing Arrangements

Operating Facilities

In 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 had 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 were only required to make interest payments. We began making principal payments in 2022. Our manufacturing facility mortgage matures in August 2027. We repaid our primary R&D facility mortgage in 2022 in conjunction with a sale and leaseback transaction.

In 2022, we concurrently entered into two purchase and sale agreements with a real estate investor. In the same period, we closed the first transaction in which we sold the facilities at our headquarters in Carlsbad, California, which includes our primary R&D facility, for a purchase price of $263.4 million. As a result, we de-recognized the related land and improvements, building and building improvements, which resulted in a net gain of $150.1 million that we reported in other income in our consolidated statements of operations. We used a portion of the sale proceeds to extinguish our outstanding mortgage debt on our primary R&D facility of $51.3 million. In connection with this transaction, we leased back our headquarters facilities for an initial lease term of 15 years with options to extend the lease for two additional terms of five years each.

In August 2023, we closed the second transaction and transferred legal ownership of two lots of undeveloped land adjacent to our headquarters to the real estate investor for a purchase price of $33 million. In connection with this transaction, we entered into a build-to-suit lease agreement with the same real estate investor to lease a new R&D facility. The lessor will develop and construct a new building composed of R&D and office space. We will design and construct tenant improvements to customize the facility's interior space. We will lease the facility for an initial term of 15 years with options to extend the lease for two additional terms of five years each. The lease will commence once the structure of this new facility is completed.

Since the building is under construction and unavailable to lease, we are unable to complete the sale-leaseback evaluation under ASC 842, Leases. As a result, the land remains in our consolidated balance sheets and we accounted for the proceeds as a financial liability. We will reassess the transaction under the sale-leaseback accounting guidance when the facilities are available for lease commencement.

Debt Maturity Schedules

Annual convertible and mortgage debt maturities, including fixed and determinable interest, at December 31, 2023 are as follows (in thousands):

2024	$ 55,298
2025	10,657
2026	643,157
2027	10,509
2028	580,277
Thereafter	8,462
Total debt and mortgage maturities	$ 1,308,360
Less: Current portion included in other current liabilities	(157)
Less: Fixed and determinable interest	(47,138)
Less: Debt issuance costs	(20,061)
Total debt	$ 1,241,004

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 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 an additional office space and warehouse space in Carlsbad. We lease these spaces under non-cancelable operating leases. In 2022, we exercised our option to extend the office space lease, extending our term from January 2023 to May 2027. We have no remaining options to extend this lease. Our warehouse space lease in Carlsbad has an initial term ending in 2028 with no options to extend the lease.

As discussed above in the section titled, *Financing Arrangements*, we lease our headquarters, which includes our primary R&D facility, as part of a sale and leaseback transaction that closed in 2022. The initial lease term for our headquarters facilities is 15 years with options to extend the lease for two additional terms of five years each. We determined at lease inception that it was not reasonably certain that we would exercise any of the options to extend the lease. We expect our lease payments over the initial term to total approximately $280 million. In connection with the transfer of legal ownership of the two lots of undeveloped land to the real estate investor, we entered into a build-to-suit lease agreement with the same real estate investor who will build a new R&D facility for us on those lots. The lease will commence once the structure of this new facility is completed.

Oceanside Lease

In 2022, we entered into a build-to-suit lease agreement to lease a development chemistry and manufacturing facility to be constructed by the lessor in Oceanside, California. We capitalized costs that we incurred related to the design and development of tenant improvements as construction-in-progress in our consolidated balance sheets. In August 2023, we reached a mutual agreement with the lessor to terminate the lease agreement. As a result, we recorded a charge of $20 million, primarily associated with the impairment of construction-in-progress assets, within SG&A expense in our consolidated statements of operations.

Boston Leases

We entered into an operating lease agreement for office space located in Boston, Massachusetts which commenced in August 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.

In 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 in January 2022. We will receive lease payments over the sublease term totaling $9.6 million.

We entered into an operating lease agreement for another office space located in Boston, Massachusetts which commenced in 2021. 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 received a seven-month free rent period, which commenced in November 2021. Our lease payments over the initial term total $6.8 million.

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 because it was not reasonably certain we would exercise those extension options.

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

	At December 31, 2023
Right-of-use operating lease assets	$ 171.9
Operating lease liabilities	$ 179.0
Weighted average remaining lease term	13.0 years
Weighted average discount rate	6.9%

During the years ended December 31, 2023, 2022, and 2021 we paid $20.1 million, $4.0 million and $3.3 million of lease payments, which were included in operating activities in our consolidated statements of cash flows.

As of December 31, 2023, the future payments for our operating lease liabilities are as follows (in thousands):

	Operating Leases
Year ending December 31,	
2024	$ 20,398
2025	20,645
2026	20,781
2027	20,800
2028	20,774
Thereafter	176,138
Total minimum lease payments	279,536
Less: Imputed interest	(100,567)
Less: Current portion (included in other current liabilities)	(8,094)
Total long-term lease liabilities	$ 170,875

Rent expense was $23.1 million, $8.3 million and $3.4 million for the years ended December 31, 2023, 2022 and 2021, respectively.

Royalty Revenue Monetization

In January 2023, we entered into a royalty purchase agreement with Royalty Pharma Investments, or Royalty Pharma, to monetize a portion of our future SPINRAZA and pelacarsen royalties we are entitled to under our agreements with Biogen and Novartis, respectively. As a result, we received an upfront payment of $500 million and we are eligible to receive up to $625 million in additional milestone payments. Under the terms of the agreement, Royalty Pharma will receive 25 percent of our SPINRAZA royalty payments from 2023 through 2027, increasing to 45 percent of royalty payments in 2028, on up to $1.5 billion in annual sales. In addition, Royalty Pharma will receive 25 percent of any future royalty payments on pelacarsen. Royalty Pharma's royalty interest in SPINRAZA will revert to us after total SPINRAZA royalty payments to Royalty Pharma reach either $475 million or $550 million, depending on the timing and occurrence of FDA approval of pelacarsen.

We recorded the upfront payment of $500 million as a liability related to the sale of future royalties, net of transaction costs of $10.4 million, which we are amortizing over the estimated life of the arrangement using the effective interest rate method. We recognize royalty revenue in the period in which the counterparty sells the related product and recognizes the related revenue. We record royalty payments made to Royalty Pharma as a reduction of the liability.

We determine the effective interest rate used to record interest expense under this agreement based on an estimate of future royalty payments to Royalty Pharma. As of December 31, 2023, the estimated effective interest rate under the agreement was 13.5 percent.

The following is a summary of our liability related to sale of future royalties for the year ended December 31, 2023 (in thousands):

Proceeds from sale of future royalties	$ 500,000
Royalty payments to Royalty Pharma	(44,628)
Interest expense related to sale of future royalties	68,238
Liability related to sale of future royalties as of December 31, 2023	523,610
Issuance costs related to sale of future royalties	(10,434)
Amortization of issuance costs related to sale of future royalties as of December 31, 2023	560
Net liability related to sale of future royalties as of December 31, 2023	$ 513,736

There are numerous factors, most of which are not within our control, that could materially impact the amount and timing of royalty payments from Biogen and Novartis, and result in changes to our estimate of future royalty payments to Royalty Pharma. Such factors include, but are not limited to, the commercial sales of SPINRAZA, the regulatory approval and commercial sales of pelacarsen, competing products or other significant events.

8. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15 million shares of "blank check" Preferred Stock. As of December 31, 2023, 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, 2023.

Common Stock

At December 31, 2023 and 2022, we had 300 million shares of common stock authorized, of which 144.3 million and 142.1 million were issued and outstanding, respectively. As of December 31, 2023, total common shares reserved for future issuance were 49.7 million.

During the years ended December 31, 2023, 2022 and 2021, we issued 2.3 million, 1.2 million and 1.1 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 $49.4 million, $6.4 million and $11.6 million in 2023, 2022 and 2021, respectively.

Stock Plans

1989 Stock Option Plan

In 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 Stock Option Plan, or 1989 Plan, does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. At December 31, 2023, no options were outstanding and 68,000 shares were available for future grant under the 1989 Plan.

2011 Equity Incentive Plan

In 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 June 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. In June 2023, after receiving approval from our stockholders, we amended our 2011 Plan to increase the total number of shares of common stock authorized for issuance under the 2011 Plan from 29.7 million to 35.2 million.

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, 2023, a total of 12.8 million options were outstanding, of which 8.7 million were exercisable, 3.3 million restricted stock unit awards were outstanding, and 8.0 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. 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, and vice presidents. If one of our executive officers or vice presidents is terminated or 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 employee's 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 2020, we assumed the unallocated portion of the available share reserve under the Akcea 2015 Equity Incentive Plan. In 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, 2023, a total of 0.4 million options were outstanding, of which 0.1 million were exercisable, 0.2 million restricted stock unit awards were outstanding, and 1.0 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 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 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 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, 2023, a total of 0.9 million options were outstanding, of which 0.9 million were exercisable, 40,000 restricted stock unit awards were outstanding, and 0.5 million shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In 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, 2023. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase. During 2023, employees purchased and we issued to employees 0.1 million shares under the ESPP at a weighted average price of $30.53 per share. At December 31, 2023, there were 0.4 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, 2023 (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, 2022	14,970	$ 50.57		
Granted	2,407	$ 38.80		
Exercised	(1,444)	$ 45.06		
Cancelled/forfeited/expired	(1,842)	$ 55.90		
Outstanding at December 31, 2023	14,091	$ 48.43	4.74	$ 78,542
Exercisable at December 31, 2023	9,703	$ 52.24	3.20	$ 28,349

The weighted-average estimated fair values of options granted were $19.72, $18.66 and $24.35 for the years ended December 31, 2023, 2022 and 2021, respectively. The total intrinsic value of options exercised during the years ended December 31, 2023, 2022 and 2021 were $6.0 million, $1.4 million and $2.5 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $65.1 million, $3.6 million and $8.5 million for the years ended December 31, 2023, 2022 and 2021, respectively. For the year ended December 31, 2023, the weighted-average fair value of options exercised was $49.23. As of December 31, 2023, total unrecognized compensation cost related to non-vested stock options was $36.6 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, 2023 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2022	2,766	$ 48.30
Granted	1,707	$ 40.51
Vested	(1,055)	$ 51.64
Cancelled/forfeited	(179)	$ 42.90
Non-vested at December 31, 2023	3,239	$ 43.40

For the years ended December 31, 2023, 2022 and 2021, the weighted-average grant date fair value of RSUs granted was $40.51, $36.14 and $57.02 per RSU, respectively. As of December 31, 2023, total unrecognized compensation cost related to RSUs was $53.7 million. We expect to recognize this cost over a weighted average period of 1.3 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Performance Restricted Stock Unit Activity

The following table summarizes the PRSU activity for the year ended December 31, 2023 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2022	143	$ 52.59
Granted	158	$ 57.43
Vested	(75)	$ 52.43
Non-vested at December 31, 2023	226	$ 56.04

For the years ended December 31, 2023, 2022 and 2021, the weighted-average grant date fair value of PRSUs granted was $57.43, $42.28 and $77.17 per PRSU, respectively. As of December 31, 2023, total unrecognized compensation cost related to PRSUs was $4.4 million. We expect to recognize this cost over a weighted average period of 1.4 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, 2023, 2022 and 2021 (in thousands):

	Year Ended December 31,		
	2023	2022	2021
Cost of sales	$ 499	$ 533	$ 456
Research, development and patent	77,826	73,704	87,522
Selling, general and administrative	27,484	26,027	32,700
Total	$ 105,809	$ 100,264	$ 120,678

Refer to Note 1, *Organization and Significant Accounting Policies*, for further details on how we determine the fair value of stock options granted, RSUs, PRSUs and stock purchase rights under the ESPP.

For the years ended December 31, 2023, 2022 and 2021, we used the following weighted-average assumptions in our Black-Scholes calculations:

Employee Stock Options:

	Year Ended December 31,		
	2023	2022	2021
Risk-free interest rate	3.8%	2.1%	0.6%
Dividend yield	0.0%	0.0%	0.0%
Volatility	46.8%	54.5%	54.0%
Expected life	6.3 years	6.3 years	4.9 years

Board of Director Stock Options:

	Year Ended December 31,		
	2023	2022	2021
Risk-free interest rate	3.8%	2.9%	1.2%
Dividend yield	0.0%	0.0%	0.0%
Volatility	52.7%	56.2%	55.9%
Expected life	7.7 years	7.4 years	7.3 years

ESPP:

	Year Ended December 31,		
	2023	2022	2021
Risk-free interest rate	5.3%	1.2%	0.1%
Dividend yield	0.0%	0.0%	0.0%
Volatility	36.0%	50.1%	42.4%
Expected life	6 months	6 months	6 months

Risk-Free Interest Rate. We base the risk-free interest rate assumption on observed interest rates appropriate for the term of our stock option plans or ESPP.

Dividend Yield. We base the dividend yield assumption on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future.

Volatility. We use an average of the historical stock price volatility of our stock for the Black-Scholes model. We computed the historical stock volatility based on the expected term of the awards.

Expected Life. The expected term of stock options we have granted represents the period of time that we expect them to be outstanding. Historically, we estimated the expected term of options we have granted based on actual and projected exercise patterns. In 2021, our Compensation Committee approved an amendment to the 2011 Equity Incentive Plan, or 2011 Plan, and the 2020 Equity Incentive Plan, or 2020 Plan, that increased the contractual term of stock options granted under these plans from seven to ten years for stock options granted on January 1, 2022 and thereafter. We determined that we are unable to rely on our historical exercise data as a basis for estimating the expected life of stock options granted to employees following this change because the contractual term changed and we have no other means to reasonably estimate future exercise behavior. We therefore used the simplified method for determining the expected life of stock options granted to employees in the years ended December 31, 2023 and 2022. Under the simplified method, we calculate the expected term as the average of the time-to-vesting and the contractual life of the options. As we gain additional historical information, we will transition to calculating our expected term based on our historical 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.

9. Income Taxes

Loss before income taxes is comprised of (in thousands):

	Year Ended December 31,		
	2023	2022	2021
United States	$ (334,707)	$ (258,493)	$ (29,966)
Foreign	742	508	818
Loss before income taxes	$ (333,965)	$ (257,985)	$ (29,148)

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

	Year Ended December 31,		
	2023	2022	2021
Current:			
Federal	$ 35,861	$ 10,522	$ (200)
State	(3,687)	1,129	(690)
Foreign	147	86	339
Total current income tax expense (benefit)	32,321	11,737	(551)
Deferred:			
Federal	—	—	—
State	—	—	—
Total deferred income tax benefit	—	—	—
Total income tax expense (benefit)	$ 32,321	$ 11,737	$ (551)

Our expense (benefit) for income taxes differs from the amount computed by applying the U.S. federal statutory rate to loss before income taxes. The sources and tax effects of the differences are as follows (in thousands):

	Year Ended December 31,					
	2023		2022		2021	
Pre-tax loss	$ (333,965)		$ (257,985)		$ (29,148)	
Statutory rate	(70,133)	21.0%	(54,177)	21.0%	(6,121)	21.0%
State income tax net of federal benefit	(22,597)	6.8%	(13,622)	5.3%	4,278	(14.7)%
Foreign	(22)	0.0%	(49)	0.0%	143	(0.5)%
Net change in valuation allowance	175,388	(52.5)%	104,951	(40.7)%	2,885	(9.9)%
Loss on debt transactions	—	—	—	—	262	(0.9)%
Tax credits	(67,131)	20.1%	(39,729)	15.4%	(23,198)	79.6%
Deferred tax true-up	4	0.0%	(20)	0.0%	(24)	0.1%
Tax rate change	1,023	(0.3)%	(3,091)	1.2%	12,838	(44.0)%
Non-deductible compensation	3,814	(1.1)%	3,023	(1.2)%	5,085	(17.4)%
Other non-deductible items	327	(0.1)%	57	0.0%	84	(0.3)%
Foreign-derived intangible income benefit	(7,493)	2.2%	—	—	—	—
Stock-based compensation	19,546	(5.9)%	14,030	(5.4)%	4,720	(16.2)%
Other	(405)	0.1%	364	(0.1)%	(1,503)	5.1%
Effective rate	$ 32,321	(9.7)%	$ 11,737	(4.5)%	$ (551)	1.9%

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, 2023 and 2022 are as follows (in thousands):

	Year Ended December 31,	
	2023	2022
Deferred Tax Assets:		
Net operating loss carryovers	$ 77,964	$ 87,802
Tax credits	239,962	277,436
Deferred revenue	71,683	85,700
Stock-based compensation	77,468	86,983
Intangible and capital assets	104,380	104,649
Convertible debt	16,849	34,384
Capitalized research and development expenses	238,738	119,635
Long-term lease liabilities	43,718	45,612
Sale of future royalties	144,608	—
Other	10,343	15,813
Total deferred tax assets	$ 1,025,713	$ 858,014
Deferred Tax Liabilities:		
Fixed assets	(4,166)	(4,475)
Right-of-use assets	(42,007)	(44,504)
Other	(1,910)	(313)
Net deferred tax asset	$ 977,630	$ 808,722
Valuation allowance	(977,630)	(808,722)
Total net deferred tax assets and liabilities	$ —	$ —

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.

Our valuation allowance increased by $169 million from December 31, 2022 to December 31, 2023. The increase was primarily related to increases in our deferred tax assets for capitalized research and development expenses and sale of future royalties.

At December 31, 2023, we had federal and state, primarily California, tax net operating loss carryforwards of $242.8 million and $398.8 million, respectively. Our federal tax loss carryforwards are available indefinitely. Our California tax loss carryforwards will begin to expire in 2032. At December 31, 2023, we also had federal and California research and development tax credit carryforwards of $169.7 million and $124.4 million, respectively. Our federal research and development tax credit carryforwards will begin to expire in 2038. Our California research and development tax credit carryforwards are available indefinitely. Our 2023 current tax expense includes a benefit of approximately $3.2 million related to utilization of state tax loss carryforwards, primarily California.

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,		
	2023	2022	2021
Beginning balance of unrecognized tax benefits	$ 56,567	$ 55,085	$ 54,163
Decrease for lapse of statute of limitations	(14,993)	—	—
Decrease for prior period tax positions	(737)	(267)	(695)
Increase for prior period tax positions	429	259	263
Increase for current period tax positions	2,032	1,490	1,354
Ending balance of unrecognized tax benefits	$ 43,298	$ 56,567	$ 55,085

Included in the balance of unrecognized tax benefits at December 31, 2023, 2022 and 2021 was $0.3 million, $6.2 million and $6.2 million respectively, that if we recognized, could impact our effective tax rate, subject to our remaining valuation allowance.

We estimate that it is reasonably possible that the balance of our gross unrecognized tax benefits may decrease by approximately $7.6 million within the next 12 months due to the lapse of statute of limitations on underlying tax positions primarily related to amortization of certain capitalized state research and development expenditures.

We recognize interest and/or penalties related to income tax matters in income tax expense. During the years ended December 31, 2023, 2022 and 2021, we recognized $0.1 million, $0.8 million and $0.5 million, respectively, of accrued interest and penalties related to gross unrecognized tax benefits.

We are subject to taxation in the U.S. and various state and foreign jurisdictions. U.S. tax years 2020 through 2022 remain open to examination and tax years 2019 through 2022 remain open to examination by major state taxing jurisdictions, primarily California, although net operating loss and credit carryforwards generated prior to these periods may still be adjusted upon examination by the Internal Revenue Service or state tax authorities if they have been used in an open period or are used in a future period.

10. Employment Benefits

We have employee 401(k) salary deferral plans covering all employees. Employees could make contributions by withholding a percentage of their salary up to the IRS annual limits of $22,500 and $30,000 in 2023 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $7.1 million, $5.6 million and $5.5 million in matching contributions for the years ended December 31, 2023, 2022 and 2021, respectively.

11. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If we consider the potential loss from any legal proceeding to be probable and we can reasonably estimate the amount, we accrue a liability for the estimated loss. The outcome of any proceeding is not determinable in advance. Therefore, we are required to use significant judgment to determine the probability of a loss and whether the amount of the loss is reasonably estimable. Our assessment of a potential liability and the amount of accruals we 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.

There are no pending material legal proceedings to which we are a party or of which our property is the subject.

12. Fourth Quarter Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized fourth quarter data for 2023 and 2022 are as follows (in thousands, except per share data).

Three Months Ended December 31,	**2023**	**2022**
Revenue (1)	$ 324,505	$ 151,890
Operating expenses (2)	$ 330,627	$ 359,909
Loss from operations	$ (6,122)	$ (208,019)
Net loss (3)	$ (9,263)	$ (52,430)
Basic net loss per share (4) (5)	$ (0.06)	$ (0.37)
Diluted net loss per share (4) (6)	$ (0.06)	$ (0.37)

(1) Revenue was higher in the three months ended December 31, 2023 compared to the same period in 2022 primarily due to the $50 million milestone payment we earned from AstraZeneca when the FDA approved WAINUA for ATTRv-PN in the U.S., $36 million payment we earned when AstraZeneca licensed ION826 and revenue we recognized in the fourth quarter of 2023 from the upfront payments we received from our new collaborations with Otsuka, Roche and Novartis.

(2) Operating expenses were lower in the three months ended December 31, 2023 compared to the same period in 2022 primarily due to the $80 million upfront payment we made for our collaboration with Metagenomi in the fourth quarter of 2022.

(3) Our net loss for the three months ended December 31, 2022 includes the $150.1 million gain we recognized from the sale and leaseback transaction for our headquarters in Carlsbad, California.

(4) We compute net loss per share independently for each quarter during the year.

(5) As discussed in Note 1, *Organization and Significant Accounting Policies,* we compute basic net loss per share by dividing the total net loss by our weighted-average number of common shares outstanding during the period.

(6) We incurred a net loss for the fourth quarter of 2023 and 2022. As a result, 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.

Exhibit 10.3

INDEMNITY AGREEMENT

THIS INDEMNITY AGREEMENT (the "***Agreement***") is made and entered into this **[DAY] day of [MONTH], [YEAR]** by and between Ionis Pharmaceuticals, Inc., a Delaware corporation (the "***Company***"), and **[DIRECTOR/OFFICER NAME]** ("***Agent***").

RECITALS

WHEREAS, Agent performs a valuable service to the Company in [his/her] capacity as [**TITLE**];

WHEREAS, the stockholders of the Company have adopted bylaws (the "***Bylaws***") providing for the indemnification of the directors, officers, employees and other agents of the Company, including persons serving at the request of the Company in such capacities with other corporations or enterprises, as authorized by the Delaware General Corporation Law, as amended ("***Delaware Law***");

WHEREAS, the Bylaws and Delaware Law by their non-exclusive nature, permit contracts between the Company and its agents, officers, employees and other agents with respect to indemnification of such persons; and

WHEREAS, in order to induce Agent to continue to serve as [**TITLE**], the Company has determined and agreed to enter into this Agreement with Agent;

NOW, THEREFORE, in consideration of Agent's continued service [**TITLE**], after the date hereof, the parties hereto agree as follows:

AGREEMENT

1. Services to the Company. Agent will serve, at the will of the Company or under separate contract, if any such contract exists, as [**TITLE**] or as a director, officer or other fiduciary of an affiliate of the Company (including any employee benefit plan of the Company) faithfully and to the best of [his/her] ability so long as she is duly elected and qualified in accordance with the provisions of the Bylaws or other applicable charter documents of the Company or such affiliate; provided, however, that Agent may at any time and for any reason resign from such position (subject to any contractual obligation that Agent may have assumed apart from this Agreement) and that the Company or any affiliate shall have no obligation under this Agreement to continue Agent in any such position.

2. Indemnity of Agent. The Company hereby agrees to hold harmless and indemnify Agent to the fullest extent authorized or permitted by the provisions of the Bylaws and Delaware Law, as the same may be amended from time to time (but, only to the extent that such amendment permits the Company to provide broader indemnification rights than the Bylaws or Delaware Law permitted prior to adoption of such amendment).

3. Additional Indemnity. In addition to and not in limitation of the indemnification otherwise provided for herein, and subject only to the exclusions set forth in Section 4 hereof, the Company hereby further agrees to hold harmless and indemnify Agent:

(a) against any and all expenses (including attorneys' fees), witness fees, damages, judgments, fines and amounts paid in settlement and any other amounts that Agent becomes legally obligated to pay because of any claim or claims made against or by her in connection with any threatened, pending or completed action, suit or proceeding, whether civil, criminal, arbitrational, administrative or investigative (including an action by or in the right of the Company) to which Agent is, was or at any time becomes a party, or is threatened to be made a party, because of the fact that Agent is, was or at any time becomes a director, officer, employee or other agent of Company, or is or was serving or at any time serves at the request of the Company as a director, officer, employee or other agent of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise; and

(b) otherwise to the fullest extent as may be provided to Agent by the Company under the non-exclusivity provisions of Delaware Law and Section 42 of the Bylaws.

4. Limitations on Additional Indemnity. No indemnity pursuant to Section 3 hereof shall be paid by the Company:

(a) on account of any claim against Agent for an accounting of profits made from the purchase or sale by Agent of securities of the Company pursuant to the provisions of Section 16(b) of the Securities Exchange Act of 1934 and amendments thereto or similar provisions of any federal, state or local statutory law;

(b) on account of Agent's conduct that was knowingly fraudulent or deliberately dishonest or that constituted willful misconduct;

(c) on account of Agent's conduct that constituted a breach of Agent's duty of loyalty to the Company or resulted in any personal profit or advantage to which Agent was not legally entitled;

(d) for which payment is actually made to Agent under a valid and collectible insurance policy or under a valid and enforceable indemnity clause, bylaw or agreement, except in respect of any excess beyond payment under such insurance, clause, bylaw or agreement;

(e) if indemnification is not lawful (and, in this respect, both the Company and Agent have been advised that the Securities and Exchange Commission believes that indemnification for liabilities arising under the federal securities laws is against public policy and is, therefore, unenforceable and that claims for indemnification should be submitted to appropriate courts for adjudication); or

(f) in connection with any proceeding (or part thereof) initiated by Agent, or any proceeding by Agent against the Company or its directors, officers, employees or other agents, unless (i) such indemnification is expressly required to be made by law, (ii) the proceeding was authorized by the Board of Directors of the Company, (iii) such indemnification is provided by the Company, in its sole discretion, pursuant to the powers vested in the Company under Delaware Law, or (iv) the proceeding is initiated pursuant to Section 9 hereof.

5. Continuation of Indemnity. All agreements and obligations of the Company contained herein shall continue during the period Agent is a director, officer, employee or other agent of the Company (or is or was serving at the request of the Company as a director, officer, employee or other agent of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise) and shall continue thereafter so long as Agent shall be subject to any possible claim or threatened, pending or completed action, suit or proceeding, whether civil, criminal, arbitrational, administrative or investigative, by reason of the fact that Agent was serving in the capacity referred to herein.

6. Partial Indemnification. Agent shall be entitled under this Agreement to indemnification by the Company for a portion of the expenses (including attorneys' fees), witness fees, damages, judgments, fines and amounts paid in settlement and any other amounts that Agent becomes legally obligated to pay in connection with any action, suit or proceeding referred to in Section 3 hereof even if not entitled hereunder to indemnification for the total amount thereof, and the Company shall indemnify Agent for the portion thereof to which Agent is entitled.

7. Notification and Defense of Claim. Not later than thirty (30) days after receipt by Agent of notice of the commencement of any action, suit or proceeding, Agent will, if a claim in respect thereof is to be made against the Company under this Agreement, notify the Company of the commencement thereof; but the omission so to notify the Company will not relieve it from any liability which it may have to Agent otherwise than under this Agreement. With respect to any such action, suit or proceeding as to which Agent notifies the Company of the commencement thereof:

(a) the Company will be entitled to participate therein at its own expense;

(b) except as otherwise provided below, the Company may, at its option and jointly with any other indemnifying party similarly notified and electing to assume such defense, assume the defense thereof, with counsel reasonably satisfactory to Agent. After notice from the Company to Agent of its election to assume the defense thereof, the Company will not be liable to Agent under this Agreement for any legal or other expenses subsequently incurred by Agent in connection with the defense thereof except for reasonable costs of investigation or otherwise as provided below. Agent shall have the right to employ separate counsel in such action, suit or proceeding but the fees and expenses of such counsel incurred after notice from the Company of its assumption of the defense thereof shall be at the expense of Agent unless (i) the employment of counsel by Agent has been authorized by the Company, (ii) Agent shall have reasonably concluded that there may be a conflict of interest between the Company and Agent in the conduct of the defense of such action or (iii) the Company shall not in fact have employed counsel to assume the defense of such action, in each of which case the fees and expenses of Agent’s separate counsel shall be at the expense of the Company. The Company shall not be entitled to assume the defense of any action, suit or proceeding brought by or on behalf of the Company or as to which Agent shall have made the conclusion provided for in clause (ii) above; and

(c) the Company shall not be liable to indemnify Agent under this Agreement for any amounts paid in settlement of any action or claim effected without the Company's written consent, which shall not be unreasonably withheld. The Company shall be permitted to settle any action except that it shall not settle any action or claim in any manner which would impose any penalty or limitation on Agent without Agent's written consent, which may be given or withheld in Agent's sole discretion.

8. Expenses. The Company shall advance, prior to the final disposition of any proceeding, promptly following request therefor, all expenses incurred by Agent in connection with such proceeding upon receipt of an undertaking by or on behalf of Agent to repay said amounts if it shall be determined ultimately that Agent is not entitled to be indemnified under the provisions of this Agreement, the Bylaws, Delaware Law or otherwise.

9. Enforcement. Any right to indemnification or advances granted by this Agreement to Agent shall be enforceable by or on behalf of Agent in any court of competent jurisdiction if (i) the claim for indemnification or advances is denied, in whole or in part, or (ii) no disposition of such claim is made within ninety (90) days of request therefor. Agent, in such enforcement action, if successful in whole or in part, shall also be entitled to be paid the expense of prosecuting her claim. It shall be a defense to any action for which a claim for indemnification is made under Section 7 hereof (other than an action brought to enforce a claim for expenses pursuant to Section 8 hereof, provided that the required undertaking has been tendered to the Company) that Agent is not entitled to indemnification because of the limitations set forth in Section 4 hereof. Neither the failure of the Company (including its Board of Directors or its stockholders) to have made a determination prior to the commencement of such enforcement action that indemnification of Agent is proper in the circumstances, nor an actual determination by the Company (including its Board of Directors or its stockholders) that such indemnification is improper shall be a defense to the action or create a presumption that Agent is not entitled to indemnification under this Agreement or otherwise.

10. Subrogation. In the event of payment under this Agreement, the Company shall be subrogated to the extent of such payment to all of the rights of recovery of Agent, who shall execute all documents required and shall do all acts that may be necessary to secure such rights and to enable the Company effectively to bring suit to enforce such rights.

11. Non-Exclusivity of Rights. The rights conferred on Agent by this Agreement shall not be exclusive of any other right which Agent may have or hereafter acquire under any statute, provision of the Company's Certificate of Incorporation or Bylaws, agreement, vote of stockholders or directors, or otherwise, both as to action in her official capacity and as to action in another capacity while holding office.

12. Survival of Rights.

(a) The rights conferred on Agent by this Agreement shall continue after Agent has ceased to be a director, officer, employee or other agent of the Company or to serve at the request of the Company as a director, officer, employee or other agent of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise and shall inure to the benefit of Agent's heirs, executors and administrators.

(b) The Company shall require any successor (whether direct or indirect, by purchase, merger, consolidation or otherwise) to all or substantially all of the business or assets of the Company, expressly to assume and agree to perform this Agreement in the same manner and to the same extent that the Company would be required to perform if no such succession had taken place.

13. Separability. Each of the provisions of this Agreement is a separate and distinct agreement and independent of the others, so that if any provision hereof shall be held to be invalid for any reason, such invalidity or unenforceability shall not affect the validity or enforceability of the other provisions hereof. Furthermore, if this Agreement shall be invalidated in its entirety on any ground, then the Company shall nevertheless indemnify Agent to the fullest extent provided by the Bylaws, Delaware Law or any other applicable law.

14. Governing Law. This Agreement shall be interpreted and enforced in accordance with the laws of the State of Delaware.

15. Amendment and Termination. No amendment, modification, termination or cancellation of this Agreement shall be effective unless in writing signed by both parties hereto.

16. Identical Counterparts. This Agreement may be executed in one or more counterparts, each of which shall for all purposes be deemed to be an original but all of which together shall constitute but one and the same Agreement. Only one such counterpart need be produced to evidence the existence of this Agreement.

17. Headings. The headings of the sections of this Agreement are inserted for convenience only and shall not be deemed to constitute part of this Agreement or to affect the construction hereof.

18. Notices. All notices, requests, demands and other communications hereunder shall be in writing and shall be deemed to have been duly given (i) upon delivery if delivered by hand to the party to whom such communication was directed or (ii) upon the third business day after the date on which such communication was mailed if mailed by certified or registered mail with postage prepaid:

(a) If to Agent, at the address indicated on the signature page hereof.

(b) If to the Company, to
Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: General Counsel
legalnotices@ionisph.com

or to such other address as may have been furnished to Agent by the Company.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement on and as of the day and year first above written.

IONIS PHARMACEUTICALS, INC.

By: _____
Name: Brett Monia
Title: Chief Executive Officer

AGENT

By: _____
Name:
Address:

Schedule of Directors and Executive Officers
with Indemnity Agreements

Joseph T. Baroldi, M.A., M.B.A., M.S., Executive Vice President, Chief Business Officer
C. Frank Bennett, Ph.D., Executive Vice President, Chief Scientific Officer
Spencer R. Berthelsen, M.D., Director
Brian Birchler, Executive Vice President, Corporate and Development Operations
Onaiza Cadoret-Manier, Executive Vice President, Chief Global Product Strategy and Operations Officer
Allene M. Diaz, Director
Richard S. Geary, Ph.D., Executive Vice President, Chief Development Officer
Michael Hayden, C.M., O.B.C., M.B., Ch.B., Ph.D., F.R.C.P.(C), F.R.S.C., Director
Joan E. Herman, Director
Elizabeth L. Hougen, Executive Vice President and Chief Financial Officer
Joseph Klein, III, Director
Joseph Loscalzo, M.D., Ph.D., Chairman of the Board
Brett P. Monia, Ph.D., Chief Executive Officer, Director
Patrick R. O'Neil, Esq., Chief Legal Officer and General Counsel
B. Lynne Parshall, Esq., Director
Eugene Schneider, M.D., Executive Vice President, Chief Clinical Development and Operations Officer
Eric E. Swayze, Ph.D., Executive Vice President, Research
Joseph H. Wender, Director
Michael Yang, Director

Exhibit 10.25

FIRST AMENDMENT TO AMENDED AND RESTATED LEASE

THIS FIRST AMENDMENT TO AMENDED AND RESTATED LEASE (this "**Amendment**") is entered into as of November 6, 2023, by and between **LOTS 21 & 22 OWNER (DE) LLC**, a Delaware limited liability company ("**Landlord**"), and **IONIS PHARMACEUTICALS, INC.**, a Delaware corporation ("**Tenant**").

R E C I T A L S:

A. Landlord and Tenant are parties to that certain Amended and Restated Lease Agreement dated as of August 21, 2023 (the "**Lease**") for certain premises consisting of approximately 164,757 gross square feet, all located within Lots 21 & 22, Whiptail Loop W in Carlsbad, California 92010 (the "**Premises**").

B. In connection therewith, Landlord and Tenant desire to amend the Lease as set forth below.

A G R E E M E N T:

NOW, THEREFORE, in consideration of the mutual covenants contained herein and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, Landlord and Tenant agree to amend the Lease as follows:

1. **Work Letter**. Schedule 9 to Exhibit B of the Lease titled "LCW by Tenant and TI by Landlord" regarding the Landlord's Construction Work by Tenant and the Tenant Improvements by Landlord is hereby deleted in its entirety and replaced with the revised Schedule 9 titled "LCW by Tenant and TI by Landlord" attached hereto as Exhibit 1.

2. **Miscellaneous**. Except as modified herein, the Lease and all of the terms and provisions thereof shall remain unmodified and in full force and effect as originally written. In the event of any conflict or inconsistency between the provisions of the Lease and the provisions of this Amendment, the provisions of this Amendment shall control. All terms used herein but not defined herein which are defined in the Lease shall have the same meaning for purposes hereof as they do for purposes of the Lease. The Recitals set forth above in this Amendment are hereby incorporated by this reference. This Amendment shall be binding upon and shall inure to the benefit of the parties hereto and their respective beneficiaries, successors and assigns. It is understood and acknowledged that there are no oral agreements between the parties hereto affecting the matters set forth in this Amendment and this Amendment constitutes the parties' entire agreement with respect to the matters set forth in this Amendment and supersedes and cancels any and all previous negotiations, arrangements, agreements and understandings, if any, between the parties hereto or with respect to the subject matter thereof, and none thereof shall be used to interpret or construe this Amendment.

3. **Counterparts**. This Amendment may be executed in any number of original or electronic counterparts which shall be treated as originals for all purposes, and by each of the undersigned on separate counterparts, which counterparts taken together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the undersigned have executed this Amendment as of the day and year first above written.

LANDLORD:

LOTS 21 & 22 OWNER (DE) LLC,
a Delaware limited liability company

By: */s/ Tycho Suter*
Name: Tycho Suter
Title: Vice President

By: */s/ Kristen Binck*
Name: Kristen Binck
Title: Vice President

TENANT:

IONIS PHARMACEUTICALS, INC.,
a Delaware corporation

By: */s/ Beth Hougen*
Name: Beth Hougen
Title: CFO

EXHIBIT 1

Schedule 9 (to Exhibit B)

LCW by Tenant and TI by Landlord

[ATTACHED]

IONIS - BTS

SCHEDULE 9 - EXECUTIVE SUMMARY
PUBLISH DATE 9/29/2023

		ANTICIPATED CONTRACT AMOUNT FOR GENERAL CONTRACTOR ($)	LANDLORD HELD CONTINGENCY ($) 5%	BUILDER'S RISK INSURANCE COSTS ($)	TOTAL ($)
CORE & SHELL	TI BY LANDLORD	$ 2,348,176	$ 117,409	$ 377,083	$ 2,842,668
WARMUP	LCW BY TENANT	$ 9,934,548	$ 496,727	$ -	$ 10,431,276

IONIS - BTS

SCHEDULE 9 - LCW BY TENANT (WARMUP)
PUBLISH DATE 9/29/2023

LCW BY TENANT			
ITEM NUMBER	**ITEM DESCRIPTION**	**COSTS ($)**	**REMARKS**
1	BNB Warmup Budget (publish date 8/31/23)	$ 12,001,004	Ref. Item # 2 onward for more detail. Includes all indirect costs. Adjusted for credit for utility sets
2	Tonnage increase - 1163 on to 1350 ton	$ (451,506)	Tenant requested change to increase capacity from Schedule 8. Includes all indirect costs.
3	Heating hot water from 5,800 MBH to 9,500 MBH	$ (392,156)	Tenant requested change to increase capacity from Schedule 8. Includes all indirect costs.
4	Office & Lab Exhaust	$ (582,445)	Tenant requested change to increase capacity from Schedule 8. Includes all indirect costs.
5	Credit for utility sets	$ (314,314)	Approved value engineering option. Includes all indirect costs. $464K total credit for utility sets. Tenant allocation of credit ~$150K.
6	Equipment Premium	$ (326,035)	Tenant requested equipment selection premium costs for Daikin ILO York (Chillers); Parker ILO Cleaver Brooks (Condensing Boilers); BAC ILO Morely (Cooling Towers). Includes all indirect costs.
TOTAL COSTS		$ 9,934,548	

IONIS - BTS
SCHEDULE 9 - TI BY LANDLORD (C&S)
PUBLISH DATE 9/29/2023

TI BY LANDLORD			
ITEM NUMBER	**DESCRIPTION**	**COSTS ($)**	**REMARKS**
1	Underground package to Building - site electrical	$ 207,990	Tenant requested change for second electrical service
2	Building passenger elevator (1 cab) upgraded from 3,500# capacity to 5,000#	$ 133,202	Tenant requested change
3	TI underground piping in C&S permitting package (not included WU underground sanitary)	$ 535,377	Tenant requested change
4	Emergency Electrical service for 50/50 (office/lab) split above SW/SF on lab SF	$ 444,716	Tenant requested change
5	Fire suppression deduct to remove upturned heads and mains	$ -	Included in Landlord scope
6	Structural dunnage above roof of AHUs (concrete pads at roof)	$ 31,178	Tenant requested change
7	Exterior changes to curtain wall	$ 140,000	Includes BNB indirect costs
8	Depressed slabs (Lobby / Restrooms)	$ 2,857	Tenant requested change
9	Delta A - 1/2 cost of Delta A Roof top Pump Room	$ 170,514	Tenant requested change
10	Delta C - Structural Changes	$ 288,386	Tenant requested change
11	Control area fire rating changes	$ 215,240	Tenant requested change
12	East Electrical Room - Walls/DFH/FSD	$ 49,058	Tenant requested change for second electrical room
13	L3 Slab Extension	$ 1,959	Tenant requested change
14	Exterior skin modifications to accommodate CO2 + LN refill requirements	$ -	Door / opening move only, no cost impact, caught early during design coordination
15	Delta A - 1/2 cost of thickened slab edge	$ 127,699	Tenant requested change
SUBTOTAL BNB COSTS		$ 2,348,176	
16	Builders Risk Insurance	$ 377,083	Based on 51% (Landlord) / 49% (Tenant) split
TOTAL COST		$ 2,725,259	

Exhibit 10.80

Execution Version

Certain portions of this exhibit, marked by [***], have been excluded because they are both not material and are the type that the registrant treats as private or confidential.

License Agreement

By and Between

Ionis Pharmaceuticals, Inc.

and

Otsuka Pharmaceutical Co., Ltd.

Dated December 15, 2023

TABLE OF CONTENTS

LICENSE AGREEMENT

This **License Agreement** (this "***Agreement***") is made and entered into as of December 15, 2023 (the "***Effective Date***") between **Ionis Pharmaceuticals, Inc.**, a Delaware corporation, having its principal place of business at 2855 Gazelle Court, Carlsbad CA 92010 USA ("***Ionis***"), and Otsuka Pharmaceutical Co., Ltd., a company organized and existing under the laws of Japan, having a place of business at 2-9, Kanda Tsukasa-machi, Chiyoda-ku, Tokyo 101-8535, Japan ("***Otsuka***"). Ionis and Otsuka may be referred to in this Agreement individually as a "***Party***" and collectively as the "***Parties***." Capitalized terms used in this Agreement, whether used in the singular or the plural, have the meaning set forth in Appendix 1 (Definitions). All attached appendices and schedules are a part of this Agreement.

RECITALS

WHEREAS, Ionis possesses certain Patent Rights, Know-How, technology and expertise with respect to research, development, and manufacturing of drugs for the treatment of HAE, and has regulatory and commercial capabilities in the Ionis Territory;

WHEREAS, Otsuka (itself and through its Affiliates) has expertise in the development and commercialization of biopharmaceutical products and has regulatory, development, and commercial capabilities in the Otsuka Territory; and

WHEREAS, the Parties desire to collaborate to Develop and Commercialize the Licensed Products, and Ionis wishes to grant Otsuka and Otsuka wishes to receive an exclusive license to Develop and Commercialize the Licensed Products in the Otsuka Territory, in each case, as set forth in, and subject to the terms of, this Agreement.

NOW THEREFORE, the Parties agree as follows:

ARTICLE 1
OVERVIEW

1.1 **Development and Commercialization**. As of the Effective Date, Ionis is Developing a Licensed Product in ongoing Clinical Trials in both the Otsuka Territory and the Ionis Territory (such studies, as further described and defined in Section 4.2.1 (Cross-Territory Clinical Development Plan)). Under this Agreement, the Parties intend (a) that Ionis will continue to conduct the Ongoing Cross-Territory Studies in accordance with the Cross-Territory Clinical Development Plan, at [***] and (b) to share the costs of all Future Cross-Territory Studies included in the Cross-Territory Clinical Development Plan as of the Effective Date and any additional Cross-Territory Clinical Studies included in any updated version of the Cross-Territory Clinical Development Plan approved by [***], in each case, in accordance with the [***]. In addition, the Parties intend for Ionis to Commercialize the Licensed Products in the Ionis Territory and Otsuka to Commercialize the Licensed Products in the Otsuka Territory, which Commercialization activities will be consistent with the global commercialization and global medical affairs strategy (as further described in Article 6 (Commercialization and Medical Affairs)).

1.2 **Governance**. The Parties have agreed to form a joint steering committee to oversee and coordinate the Development, Manufacturing, and Commercialization activities with respect to the Licensed Products under this Agreement.

1.3 **Purpose**. The purpose of this Article 1 (Overview) 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 (Overview) is qualified in its entirety by the more detailed provisions of this Agreement set forth below.

ARTICLE 2
LICENSES

2.1 **License Grants to Otsuka**. Subject to the terms of this Agreement (including Ionis' retained rights set forth in Section 2.5 (No Other Rights and Retained Rights; Negative Covenant)), Ionis hereby grants to Otsuka:

2.1.1 an exclusive, royalty-bearing license, with the right to grant sublicenses solely in accordance with Section 2.3.1(a) (Rights of Otsuka to Grant Sublicenses), under the Ionis Technology and the Unitary Product Trademark, in each case, to (a) Develop the Licensed Products in the Field in the Otsuka Territory in accordance with the Otsuka Territory-Specific Development Plan solely for Commercialization and for the conduct of Medical Affairs for such Licensed Products in the Field in the Otsuka Territory and (b) Commercialize and conduct Medical Affairs for the Licensed Products in the Field in the Otsuka Territory. For clarity, the license grant under this Section 2.1.1 (License Grants to Otsuka) does not include the right to Manufacture the Licensed Products.

2.1.2 a non-exclusive, royalty-bearing license, with the right to grant sublicenses solely in accordance with Section 2.3.1(b) (Rights of Otsuka to Grant Sublicenses), under the Ionis Technology and the Unitary Product Trademark solely to (a) Package and Label the Licensed Products in the Field in the Territory and (b) Manufacture the Licensed Products in the Field in the Territory from and after the time Otsuka provides a Manufacturing Handover Notice, in each case ((a) and (b)), solely for Commercialization and for the conduct of Medical Affairs for such Licensed Products in the Field in the Otsuka Territory.

2.2 **License Grant to Ionis**. Subject to the terms of this Agreement, including Otsuka's retained rights set forth in Section 2.5 (No Other Rights and Retained Rights; Negative Covenants), Otsuka hereby grants to Ionis an exclusive, royalty-free, fully-paid, perpetual license, with the right to grant sublicenses through multiple tiers, under the Otsuka Technology solely to (a) Develop the Licensed Products in the Ionis Territory and the Otsuka Territory; *provided* that, unless this Agreement has been terminated, any such Development in the Otsuka Territory will be conducted solely in accordance with the Cross-Territory Clinical Development Plan and the Non-Clinical HAE Development Plan, (b) Manufacture the Licensed Products worldwide in accordance with this Agreement, and (c) Commercialize the Licensed Products in the Ionis Territory in accordance with this Agreement and, subject to Section 14.9.5 (Sublicenses), worldwide following any termination of this Agreement.

2.3 **Sublicensing and Subcontracting Terms**.

2.3.1 **Rights of Otsuka to Grant Sublicenses**.

(a) Subject to the terms of this Agreement, Otsuka will have the right to grant sublicenses of the rights granted under Section 2.1.1 (License Grants to Otsuka) (i) [***], and (ii) [***].

(b) Subject to the terms of this Agreement, Otsuka will have the right to grant sublicenses of the rights granted under Section 2.1.2 (License Grants to Otsuka) (i) [***], and (ii) [***].

2.3.2 **Right to Subcontract**. Each Party may engage one or more Third Party subcontractors to perform services in furtherance of the performance of its obligations or exercise of its rights under this Agreement, including any Third Party contract manufacturer, contract research organization, contract sales organization, wholesaler or distributor (including a distributor that is engaged to conduct promotional activities with respect to the Licensed Products on such Party's behalf and under such Party's control) ("***Subcontractors***"); *provided* that (a) neither Party will engage any such Subcontractor that has been Debarred/Excluded; and (b) no engagement of any such Subcontractors will relieve the engaging Party of its obligations under this Agreement or any liability hereunder.

2.3.3 **Sublicense and Subcontract Agreements**. Each agreement pursuant to which a sublicense is granted to a Sublicensee by Otsuka pursuant to this Section 2.3 (Sublicensing and Subcontracting Terms), each agreement pursuant to which a sublicense is granted to a Sublicensee by Ionis of the rights granted to it under Section 2.2 (License Grant to Ionis), and each agreement pursuant to which a Party engages any Subcontractor, in each case after the Effective Date and during the Term, will (a) be subject and subordinate to this Agreement, (b) be consistent with the terms of this Agreement, (c) include obligations of confidentiality and non-use applicable to the Confidential Information of the other Party that are at least as stringent as those set forth in Article 12 (Confidentiality), and (d) include terms that are consistent with the intellectual property provisions set forth in this Agreement. As soon as reasonably practicable after execution of any sublicense agreement with a Sublicensee after the Effective Date, [***]. In addition, [***].

2.3.4 **Responsibility for Sublicensees and Subcontractors**. Notwithstanding any sublicense, the sublicensing or subcontracting Party will remain primarily liable to the other Party for the performance of all of its obligations under, and such Party's compliance with all provisions of, this Agreement. Each Party agrees that it will be fully responsible and liable for any breach of the terms of this Agreement by any of its Sublicensees or Subcontractors to the same extent as if such Party itself has committed any such breach.

2.4 Collaboration Technology Enabling License. Subject to the terms and conditions of this Agreement (and without limiting the licenses granted to Otsuka under Section 2.1 (License Grants to Otsuka)), Otsuka hereby grants Ionis a fully-paid, royalty-free, irrevocable, worldwide, non-exclusive, sublicensable (through multiple tiers) license under any Otsuka Collaboration Know-How and Otsuka Collaboration Patent Rights (excluding any Product-Specific Patents) to Exploit products that include an oligonucleotide as an active pharmaceutical ingredient (other than a Licensed Product); *provided* that Ionis may only grant a sublicense under the rights granted in this Section 2.4 (Collaboration Technology Enabling License) if such sublicense includes the grant of a license under Know-How or Patent Rights Controlled by Ionis or its Affiliates to Exploit such products that include an oligonucleotide as an active pharmaceutical ingredient (other than a Licensed Product).

2.5 No Other Rights and Retained Rights; Negative Covenant.

2.5.1 **No Other Rights and Retained Rights**. Nothing in this Agreement will be interpreted to grant a Party any rights under any intellectual property rights owned or Controlled by the other Party, including Ionis Technology or Otsuka Technology, in each case, that are not expressly granted herein, whether by implication, estoppel, or otherwise. Otsuka will not practice the Ionis Technology other than as expressly licensed and permitted under this Agreement and Ionis will not practice the Otsuka Technology 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. Without limiting the foregoing, (a) Ionis hereby expressly retains the right to perform (i) Development activities for the Licensed Products worldwide in accordance with the Cross-Territory Clinical Development Plan and the Non-Clinical HAE Development Plan, (ii) Manufacturing activities worldwide, and (iii) Ionis' other obligations under this Agreement, and (b) Otsuka hereby expressly retains the right to perform Development activities for the Licensed Products in the Field in the Otsuka Territory in accordance with the Otsuka Territory-Specific Development Plan solely for Commercialization and for the conduct of Medical Affairs for such Licensed Products in the Field in the Otsuka Territory and to Manufacture the Licensed Products in the Field in the Territory solely for Commercialization and for the conduct of Medical Affairs for such Licensed Products in the Field in the Otsuka Territory, in each case, in accordance with this Agreement.

2.5.2 **Negative Covenant**. Ionis shall not, and shall cause its Affiliates to not, grant or convey any right to any Third Party (pursuant to a license grant, collaboration or services agreement, option grant, or otherwise) that would be in conflict with, limit the scope of, or otherwise adversely affect the licenses granted to Otsuka pursuant to Section 2.1 (License Grants to Otsuka).

2.6 Existing Third-Party IP Agreements.

2.6.1 **Compliance**. Otsuka acknowledges and agrees that (a) the rights and licenses granted to Otsuka under this Agreement are subject to the applicable terms of all Existing Third-Party IP Agreements with respect to the Ionis Technology that is being sublicensed thereunder to Otsuka, (b) Ionis' ability to comply with its obligations, and grant rights and licenses to Otsuka, under this Agreement are limited by any and all requirements and restrictions imposed on Ionis under the Existing Third-Party IP Agreements with respect to the Ionis Technology that is being sublicensed to Otsuka by Ionis under such Existing Third-Party IP Agreements, and (c) Ionis will not be required to take any action or inaction pursuant to this Agreement that would cause Ionis to be in breach of any Existing Third-Party IP Agreement or to grant any rights to Otsuka hereunder that are in violation of, or inconsistent with, any Existing Third-Party IP Agreement. Otsuka will abide by the applicable terms of the Existing Third-Party IP Agreements, and, subject to [***], the applicable terms of any amendments, in each case, to the extent such terms are disclosed in the copies of the Existing Third-Party IP Agreements, and amendments thereto, that are provided or made available to Otsuka.

2.6.2 **Existing Third-Party IP Amendments**. During the Term, Ionis will promptly furnish Otsuka with copies of any amendment to any Existing Third-Party IP Agreement to the extent related to any of the rights sublicensed to Otsuka hereunder, from which copies Ionis may redact confidential or commercially sensitive information or other information that is not relevant to the rights sublicensed to Otsuka pursuant to the applicable Existing Third-Party IP Agreement. During the Term, Ionis shall: (a) [***]; (b) [***]; (c) [***]; and (d) [***]. Notwithstanding any provision to the contrary in this Agreement, as between the Parties, [***] shall be solely responsible for the payment of all license fees, royalties, milestone payments, and other payment obligations under all Existing Third-Party IP Agreements.

2.7 New Third-Party IP Agreements.

2.7.1 **Identification of New In-License Agreements**. If either Party intends to obtain Control of any Patent Rights or Know-How from a Third Party (whether by acquisition or license) that such Party believes are [***] to Exploit the Licensed Compound or a Licensed Product (other than in connection with a Change of Control of a Party or as a result of the acquisition by a Party of a Third Party by merger, acquisition, or similar transaction or series of related transactions) (such Patent Rights and Know-How, "***Identified Rights***"), then such Party will notify the other Party of the Identified Rights.

2.7.2 **Potential In-Licenses**.

(a) **Acquisition of Potential In-Licenses**.

i. [***] that [***] in the Exploitation of a Licensed Product in [***] Territory, whether by license or acquisition, (each agreement to license or acquire such Identified Rights, a "***Potential In-License***") in accordance with this Section 2.7.2 (Potential In-Licenses). If [***] after the Effective Date, then [***] will [***]. If [***] pursuant to this Section 2.7.2(a) (Acquisition of Potential In-Licenses), then [***] with respect to [***] to Exploit the Licensed Products. [***] such Potential In-License will [***]. [***]. If the Identified Rights to be licensed or acquired under a Potential In-License would constitute Ionis Core Technology or Ionis Manufacturing and Analytical Technology if such Identified Rights were Controlled by Ionis (any such Identified Rights, "***Core or Manufacturing Identified Rights***") then, [***] such Potential In-License (a "***Core or Manufacturing Potential In-License***") in accordance with Section 2.7.2(c)i (Non-Approved Potential In-Licenses).

ii. If either Party [***] and if the Parties [***], then [***]. At either Party's request if [***] in accordance with this Section 2.7.2(a)ii (Acquisition of Potential In-Licenses), the Parties will [***]. If the [***], then the Potential In-License [***] for all purposes of this Agreement. If [***], then Ionis will [***]. If Ionis [***] pursuant to this Section 2.7.2(a)ii (Acquisition of Potential In-Licenses) and Ionis [***] in accordance with this Section 2.7.2(a)ii (Acquisition of Potential In-Licenses), then [***]. If Ionis [***], then Otsuka will [***] in accordance with the terms of this Section 2.7.2(a)ii (Acquisition of Potential In-Licenses) and Otsuka will [***].

(b) **Collaboration In-Licenses**. For any Potential In-License that [***] in accordance with Section 2.7.2(a) (Acquisition of Potential In-Licenses), and for [***] (i) such Potential In-License will [***], (ii) the Party [***] will [***], to the extent set forth in Section 2.7.2(a)ii (Acquisition of Potential In-Licenses), (iii) the Patent Rights or Know-How in-licensed under such [***], and (iv) (A) each Party will [***], and (B) the Parties will [***]. The Party that [***] will [***] pursuant to this Section 2.7.2(b) (Collaboration In-License), and such other Party will [***].

(c) **[***] Potential In-Licenses**.

i. If [***] a Potential In-License [***], then (A) such Potential In-License [***], (B) subject to Section 2.7.2(c)ii ([***] Potential In-Licenses), the Patent Rights and Know-How in-licensed under such Potential In-License [***], (C) except as set forth in clause (D) of this Section 2.7.2(c)i ([***] Potential In-Licenses), Ionis will [***] and, subject to Section 2.7.2(c)ii ([***] Potential In-Licenses), will [***]; *provided* that if such Potential In-License [***], then [***], and Ionis [***] in accordance with Section 2.7.2(c)ii ([***] Potential In-Licenses), then Otsuka [***], and (D) if such Potential In-License (1) was [***] pursuant to Section 2.7.2(a) (Acquisition of Potential In-Licenses), (2) was not [***], and (3) is not [***], then [***] in accordance with this Agreement [***], and the terms of this Section 2.7.2 (Potential In-Licenses) [***]. If Ionis [***] in accordance with Section 2.7.2(a) (Acquisition of Potential In-Licenses), then Otsuka [***]. If [***], then Otsuka [***] in accordance with this Section 2.7.2(c)i ([***] Potential In-Licenses) and Otsuka will [***].

ii. If Ionis [***], then Ionis [***]. If Ionis [***] in accordance with Section 2.7.2(c)i ([***] Potential In-Licenses), then Ionis will [***]. Ionis may [***]. Within [***], Otsuka will [***]. If Otsuka [***] in accordance with this Section 2.7.2(c)ii ([***] Potential In-Licenses), then such [***] and Section 2.7.2(b) (Collaboration In-Licenses) will apply, *mutatis mutandis*. If Otsuka [***] in accordance with this Section 2.7.2(c)ii ([***] Potential In-Licenses), then Otsuka [***].

2.8 Right of First Negotiation for Follow-On Products.

2.8.1 **ROFN Exercise**. If, during the period from the Effective Date until the [***], Ionis intends to grant rights to a Third Party that include the right to Commercialize [***] designed to bind to the RNA encoding PKK for the treatment of HAE (any such compound, a "***Follow-On Product***") in the Otsuka Territory, then Ionis will provide to Otsuka (a) notice of the proposed scope of Commercialization rights that Ionis proposes to grant and (b) an information package containing, to the extent such information is in Ionis' or its Affiliate's Control: (i) summaries of [***] (ii) information about [***] (iii) a summary of [***] and (iv) [***] related to the Follow-On Product to the extent necessary or reasonably useful for Otsuka to evaluate whether to obtain rights with respect to Follow-On Product ("***ROFN Notice and Package***"). Promptly thereafter, Ionis will provide a high-level presentation to the JSC relating to the Follow-On Product and the rights Ionis proposes to grant. Otsuka will have an exclusive right, exercisable no later than [***] after receipt of a ROFN Notice and Package from Ionis containing all information set forth in the foregoing clauses ((i) through (iv)) to the extent such information is in Ionis' or its Affiliate's Control, to notify Ionis in writing as to whether Otsuka desires to negotiate for such rights to Commercialize such Follow-On Product in the Otsuka Territory (a "***ROFN Exercise Notice***"). During such [***], Ionis will [***].

2.8.2 **Negotiation**. If Otsuka provides a ROFN Exercise Notice to Ionis within such [***], then the Parties will negotiate in good faith for [***] from the date of Ionis' receipt of the ROFN Exercise Notice, or such longer period as may be agreed upon in writing by the Parties (the "***ROFN Negotiation Period***") the terms of a definitive agreement (or amendment to this Agreement) pursuant to which Ionis would grant to Otsuka the rights to Commercialize (and, as agreed by the Parties, to otherwise Exploit) such Follow-On Product in the Otsuka Territory. Neither Party will have any obligation to enter into any agreement or amendment to this Agreement granting rights to Otsuka to Commercialize or otherwise Exploit such Follow-On Product in the Otsuka Territory. If the ROFN Negotiation Period expires before the Parties have entered into an agreement or amendment to this Agreement with respect to Otsuka's Commercialization or other Exploitation of such Follow-On Product in the Otsuka Territory, and if such ROFN Negotiation Period [***], then Ionis will have the right to negotiate and enter into an agreement with any Third Party with respect to a grant of rights to Exploit such Follow-On Product in the Otsuka Territory [***]. If Ionis does not grant rights to a Third Party that include the right to Commercialize such Follow-On Product in the Otsuka Territory [***], then the terms of this Section 2.8 (Right of First Negotiation for Follow-On Products) will [***]. If the [***] expires before the Parties have entered into an agreement or amendment to this Agreement with respect to Otsuka's Commercialization or other Exploitation of such Follow-On Product in the Otsuka Territory, then Ionis will have no further obligation to negotiate with Otsuka with respect to any grant of such rights to Otsuka and will be free to negotiate and enter into an agreement with any Third Party with respect to a grant of rights to Exploit such Follow-On Product in the Otsuka Territory.

2.8.3 **Follow-On Product Activities**. If Ionis enters into an agreement with a Third Party granting any rights to Exploit a Follow-On Product, then all Development, Commercialization, and Medical Affairs activities related to such Follow-On Product ("***Follow-On Product Activities***") will be subject to the following: (a) [***] related to such Follow-On Product; and (b) Ionis and its Affiliates shall conduct the Follow-On Product Activities independently of the activities under this Agreement and [***].

ARTICLE 3
TECHNOLOGY TRANSFER

3.1 **Initial Know-How Transfer**. At a time period to be agreed upon by the Parties after the Effective Date, Ionis will provide and transfer, and in any event will initiate such transfer within [***] after the Effective Date, to Otsuka copies of the Ionis Know-How (other than Ionis Manufacturing and Analytical Know-How, the transfer of which will be conducted pursuant to Section 7.4 (Manufacturing Technology Transfer)) that (a) exists on the Effective Date, (b) was not previously provided to Otsuka, and (c) is [***] to Develop, Commercialize or conduct Packaging and Labeling or Medical Affairs for a Licensed Product (such transfer, the "***Initial Know-How Transfer***"). Ionis may make such Ionis Know-How available in such reasonable form as maintained by Ionis. In addition to the Initial Know-How Transfer, upon Otsuka's reasonable request during the Term, Ionis will provide and transfer to Otsuka copies of or otherwise make available to Otsuka all Ionis Know-How (other than Ionis Manufacturing and Analytical Know-How) not previously provided to Otsuka hereunder to the extent such Ionis Know-How is [***] to Develop, Commercialize or conduct Packaging and Labeling or Medical Affairs for a Licensed Product, including in accordance with Section 4.7 (Data Transfer), Section 5.6 (Cooperation), Section 6.1.2 (Commercialization in the Otsuka Territory), Section 6.2 (Commercialization and Medical Affairs Reporting), and Section 7.1.1 (Ionis Manufacturing) (the "***Continuing Know-How Transfer***," and together with the Initial Know-How Transfer, the "***Technology Transfer***").

3.2 **Technology Transfer Costs**. Ionis will conduct the Technology Transfer, and will provide consultation and assistance with [***] to provide support set forth in Section 7.1.1 (Ionis Manufacturing) (any such consultation, assistance, or support provided by [***]. Ionis will [***] in connection with the Initial Know-How Transfer, including, for clarity, [***]. In addition, Ionis will [***] in providing Requested Assistance to Otsuka in connection with such Continuing Know-How Transfer, until [***] and, thereafter, [***]. After [***]. At all times, Otsuka will [***]. Ionis may [***] following receipt of such Regulatory Approval, to the extent [***]. Ionis shall [***]. Notwithstanding the foregoing, [***]. For clarity, the terms of this Section 3.2 (Technology Transfer Costs) shall not apply with respect to [***] and, for clarity, the terms of this Section 3.2 (Technology Transfer Costs) shall not apply to [***]. Notwithstanding any provision to the contrary, Ionis' obligations to conduct the Technology Transfer and provide Requested Assistance will not require Ionis to conduct any additional Clinical Trials or generate any additional data or information that is not expressly contemplated by the Cross-Territory Clinical Development Plan or Non-Clinical HAE Development Plan.

ARTICLE 4
DEVELOPMENT

4.1 **Development Diligence Obligations**. Ionis will be responsible for conducting the activities under the Cross-Territory Clinical Development Plan and the Non-Clinical HAE Development Plan and will use Commercially Reasonable Efforts to carry out such activities. For clarity, Ionis shall not conduct any [***]. Otsuka will be responsible for conducting the activities under the Otsuka Territory-Specific Development Plan [***]. Each Party will conduct all Development activities for which it is responsible under this Agreement in a good scientific manner, in accordance with GLP and GCP, as applicable, and in compliance with Professional Requirements and Applicable Law.

4.2 **Development Plans**.

4.2.1 **Cross-Territory Clinical Development Plan**. The initial development plan for the clinical Development activities for both the Otsuka Territory and the Ionis Territory is set forth on SCHEDULE 4.2.1 (such development plan as it may be modified in accordance with the terms and conditions of this Agreement, the "***Cross-Territory Clinical Development Plan***"). The initial Cross-Territory Clinical Development Plan includes (and any updates to the Cross-Territory Clinical Development Plan will at all times include) all Clinical Trials that are intended to support obtaining or maintaining Regulatory Approval for any Licensed Product in both the Otsuka Territory and the Ionis Territory (any such Clinical Trials, "***Cross-Territory Clinical Studies***"), including (a) all Cross-Territory Clinical Studies that are ongoing as of the Effective Date (the "***Ongoing Cross-Territory Studies***"), (b) all Post-Approval Mandatory Studies that are (i) required to support maintaining Regulatory Approval for any Licensed Product in both the Otsuka Territory and the Ionis Territory and (ii) designed to meet the requirements of the EMA for maintaining Regulatory Approval of the Licensed Product in the Otsuka Territory (collectively ((i) and (ii)), "***Post-Approval Cross-Territory Mandatory Studies***"), and (c) all future Cross-Territory Clinical Studies for [***]. From time to time during the Term, either Party may submit to the JSC any proposed update to the Cross-Territory Clinical Development Plan to include additional Cross-Territory Clinical Studies, including the study designs for such additional Cross-Territory Clinical Studies. In addition, each Party shall submit to the JSC (or a designated Subcommittee) reasonably in advance proposed updates to the Cross-Territory Clinical Development Plan to take into account changed circumstances, such as cessation of any Cross-Territory Clinical Study, or the need to amend any Cross-Territory Clinical Study, including amendments in response to Regulatory Authority requirements, for safety reasons or otherwise. The JSC will review, discuss, and determine whether to approve each update to the Cross-Territory Clinical Development Plan. Once reviewed and approved by the JSC, each update to the Cross-Territory Clinical Development Plan will automatically become effective and supersede the previous Cross-Territory Clinical Development Plan, as of the date of such approval by the JSC.

4.2.2 **Non-Clinical HAE Development Plan**. The initial development plan for all CMC Development and non-clinical Development, in each case, required to obtain and maintain Regulatory Approval for the Licensed Product for the treatment of HAE in the Otsuka Territory is set forth on SCHEDULE 4.2.2 (such development plan, as it may be modified in accordance with the terms and conditions of this Agreement, the "***Non-Clinical HAE Development Plan***"). From time to time during the Term, either Party may submit to the JSC any proposed update to the Non-Clinical HAE Development Plan to include additional CMC Development or non-clinical Development activities required to obtain or maintain Regulatory Approval for the Licensed Product for the treatment of HAE in the Otsuka Territory. In addition, each Party shall submit to the JSC (or a designated Subcommittee) reasonably in advance proposed updates to take into account changed circumstances or the need to amend any CMC Development or non-clinical Development activities for the Licensed Product for the treatment of HAE in the Otsuka Territory. The JSC will review, discuss, and determine whether to approve each update to the Non-Clinical HAE Development Plan. Once reviewed and approved by the JSC, each update to the Non-Clinical HAE Development Plan will automatically become effective and supersede the previous Non-Clinical HAE Development Plan as of the date of such approval by the JSC.

4.3 Otsuka Territory-Specific Development Plan. Within [***] following the Effective Date, Otsuka will prepare and submit to the JSC a plan setting forth all Development activities that are intended to support obtaining or maintaining Regulatory Approval for the Licensed Products solely in the Otsuka Territory other than the activities set forth in the Non-Clinical HAE Development Plan (the "***Otsuka Territory-Specific Development Plan***"). The JSC will review, discuss, and determine whether to approve the Otsuka Territory-Specific Development Plan. The Otsuka Territory-Specific Development Plan will, at all times during the Term, be consistent with the then-current Cross-Territory Clinical Development Plan, except to the extent such inconsistency is (a) necessary to conform with any written requirement from any Regulatory Authority or with any Applicable Law (including compliance requirements) in the Otsuka Territory or (b) approved by the JSC (by unanimous Party Vote). At least [***] during the Term (and more frequently as may be necessary), Otsuka will prepare an update to the Otsuka Territory-Specific Development Plan to amend or include additional Development activities to be conducted during the [***] Calendar Year that are intended to support obtaining or maintaining Regulatory Approval for the Licensed Products solely in the Otsuka Territory other than the activities set forth in the Non-Clinical HAE Development Plan (or otherwise update the Development activities under the Otsuka Territory-Specific Development Plan). The JSC will review, discuss, and determine whether to approve each update to the Otsuka Territory-Specific Development Plan. Once approved by the JSC, the Otsuka Territory-Specific Development Plan and each update thereto will automatically become effective and, in the case of an update, supersede the previous Otsuka Territory-Specific Development Plan as of the date of such approval. Notwithstanding the foregoing or anything to the contrary in this Agreement, the Otsuka Territory-Specific Development Plan will at all times include Development activities that are (i) necessary to obtain and maintain Regulatory Approval for at least one Licensed Product in [***] consistent with Otsuka's obligations under Section 4.1 (Development Diligence Obligations) and (ii) not included in the Cross-Territory Clinical Development Plan or the Non-Clinical HAE Development Plan.

4.4 Development Costs.

4.4.1 **Overview**.

(a) **Ionis Costs**. Ionis will be [***] responsible for all costs and expenses incurred in connection with the performance of the [***]. In addition, Ionis will be [***] responsible for all costs and expenses incurred in connection with the performance of all activities under the [***].

(b) **Otsuka Costs**. Otsuka will be [***] responsible for all costs and expenses incurred in connection with the performance of all activities under the [***].

(c) **Shared Development Costs**. With respect to (i) all Post-Approval Cross-Territory Mandatory Studies for the treatment of HAE that are included in the Cross-Territory Clinical Development Plan as of the Effective Date] and (ii) [any other Post-Approval Cross-Territory Mandatory Studies for the treatment of HAE or any Future Cross-Territory Studies, in each case, that are added to the Cross-Territory Clinical Development Plan in accordance with Section 4.2.1 (Cross-Territory Clinical Development Plan), the Parties will share, [***], in each case, in accordance with the Cross-Territory Clinical Development Plan and Shared Development Budget (such costs, "***Shared Cross-Territory Development Costs***") in accordance with the terms of Section 4.4.3 (Shared Cross-Territory Development Costs).

4.4.2 **Shared Development Budget; Cost Overruns**.

(a) **Shared Development Budget**. The initial budget for the Shared Cross-Territory Development Costs (such budget as it may be modified in accordance with the terms and conditions of this Agreement, the "***Shared Development Budget***") for the Post-Approval Cross-Territory Mandatory Studies that are included in the Cross-Territory Clinical Development Plan as of the Effective Date is set forth in SCHEDULE 4.4.2 (Shared Development Budget). With respect to each other Post-Approval Cross-Territory Mandatory Study for the treatment of HAE or Future Cross-Territory Study that is subject to cost sharing by the Parties in accordance with Section 4.4.1(c) (Shared Development Costs), the JSC will develop, discuss, and determine whether to approve an update to the Shared Development Budget at the time the JSC reviews, discusses, and determines whether to approve the update to the Cross-Territory Clinical Development Plan applicable to such additional Cross-Territory Clinical Study. Any update to the Shared Development Budget will at all times include a detailed written budget for the performance of all Future Cross-Territory Studies and any additional Post-Approval Cross-Territory Mandatory Studies for the treatment of HAE, in each case, that are included in the Cross-Territory Clinical Development Plan (as updated). From time to time during the Term, either Party may submit to the JSC any proposed update to the Shared Development Budget, including in connection with any update to the Cross-Territory Clinical Development Plan or to address a potential Cost Overrun. The JSC will review, discuss, and determine whether to approve each update to the Shared Development Budget. Once reviewed and approved by the JSC, each update to the Shared Development Budget will automatically become effective and supersede the previous Shared Development Budget, as of the date of such approval by the JSC.

(b) **Cost Overruns**. Ionis [***] for a given Calendar Year [***] for such Calendar Year. Ionis will notify the JSC (or any designated Subcommittee) without undue delay if it reasonably anticipates that the Shared Cross-Territory Development Costs are reasonably likely to exceed the then-current Shared Development Budget by more than [***] (a "***Cost Overrun***"). Ionis will include [***] and, to the extent reasonably possible, will [***]. Thereafter, the JSC (or designated Subcommittee) shall promptly hold an ad-hoc meeting to evaluate whether there are mitigation measures to prevent the Cost Overrun, and if not, the JSC (or designated Subcommittee) will discuss what steps to take to address such Cost Overrun, including updating the Shared Development Budget or the Cross-Territory Clinical Development Plan, as applicable. If the JSC does not approve an update to the Shared Development Budget to reflect the anticipated Cost Overrun, then [***] and, to the extent [***]. For clarity, [***].

4.4.3 **Shared Cross-Territory Development Costs**. The Parties will share, at the [***], all Shared Cross-Territory Development Costs incurred by or on behalf of Ionis or its Affiliates in accordance with the Cross-Territory Clinical Development Plan and the amount budgeted therefor in the Shared Development Budget, *plus* [***] ("***Eligible Cross-Territory Development Costs***"). No later than [***] after the end of each Calendar Quarter, Ionis will deliver to Otsuka a written report specifying in reasonable detail the Eligible Cross-Territory Development Costs incurred by or on behalf of Ionis during such Calendar Quarter, together with reasonable supporting documentation (the "***Development Cost Share Notice***") and an invoice (and, if there has been any change to a Payment Form previously submitted, or if a previously submitted Payment Form has expired, an updated Payment Form) for Otsuka's [***] share of such Eligible Cross-Territory Development Costs. No later than [***] after Otsuka's receipt of the Development Cost Share Notice and invoice (and updated Payment Form, if applicable) for such Calendar Quarter, Otsuka will make a balancing payment to Ionis equal to [***] of the total Eligible Cross-Territory Development Costs to effect the [***] for such Eligible Cross-Territory Development Costs; *provided* that, if Otsuka disputes any invoiced amount, then Otsuka will pay the undisputed invoiced amount within such [***] and will pay any disputed amounts within [***] following resolution of the dispute and determination that such amounts are owed.

4.4.4 **Future Cross-Territory Studies for [***]**.

(a) **Shared Costs**. At any time during the Term, either Party may propose that the Parties clinically Develop a Licensed Product [***]. Such Party will submit a proposal to the JSC setting forth the proposed clinical Development activities for such [***] and a timeline and budget for such activities (a "[***]"). The JSC will review, discuss, and determine whether to approve such [***], either as proposed or as may be revised by agreement of the JSC, within [***] of the submission thereof. If the JSC approves such [***], as proposed or as revised per the agreement of the Parties, then (i) the JSC will approve an update to the Cross-Territory Clinical Development Plan in accordance with Section 4.2.1 (Cross-Territory Clinical Development Plan) and to the Shared Development Budget in accordance with Section 4.4.2(a) (Shared Development Budget) to include any Future Cross-Territory Studies for such [***] and (ii) the Parties will share the cost of any Eligible Cross-Territory Development Costs incurred in connection with the performance of such Future Cross-Territory Studies in accordance with Section 4.4.3 (Shared Cross-Territory Development Costs).

(b) **[***] by Ionis**. If the JSC does not approve [***] for a given [***] or does not approve an updated Cross-Territory Clinical Development Plan in accordance with Section 4.2.1 (Cross-Territory Clinical Development Plan) or Shared Development Budget in accordance with Section 4.4.2(a) (Shared Development Budget) to include the Future Cross-Territory Studies for such [***], then (i) Ionis will have the right, but not the obligation, to proceed with the Development of such [***] in the Territory as contemplated by [***] with such modifications as Ionis deems appropriate [***] ("***Ionis*** [***]") and such Development will be conducted outside the Cross-Territory Clinical Development Plan; and (ii) notwithstanding the licenses, rights of reference, and other rights granted to Otsuka under this Agreement, Otsuka will not have any license or rights to use any Ionis [***] (including any right of reference to use such Ionis [***] contained in the related Regulatory Submissions by Ionis and notwithstanding the inclusion of any such data in the Ionis Technology) in support of any Regulatory Submissions or Regulatory Approval for the Licensed Product in the Otsuka Territory or in the Commercialization of such Licensed Product in the Otsuka Territory, unless and until [***], *provided* that Otsuka may use safety data in connection with such Ionis [***] solely to satisfy any safety-related reporting obligations to Regulatory Authorities related to Licensed Products in the Otsuka Territory without [***]. For clarity, Ionis [***].

(c) **Otsuka Opt-In**. If Ionis conducts any Ionis [***] pursuant to Section 4.4.4(b) ([***] by Ionis), then Ionis shall provide Development reports to Otsuka related to such Ionis [***] in accordance with Section 4.5 (Development Reports), and Otsuka shall have the right, [***] to opt-in with respect to such Ionis [***] in accordance with this Section 4.4.4(c) (Otsuka Opt-In). Upon Otsuka's written request, Ionis shall provide to Otsuka a written report of the Internal Costs and External Costs, in each case, incurred directly by or on behalf of Ionis or its Affiliates as of the date of such written request in the performance of such Ionis [***] (the "***Ionis*** [***] ***Costs***"). Such written report shall include supporting documentation of the External Costs included within the Ionis [***] Costs. Otsuka shall have the right, exercisable during the [***] period after receipt of such report, to provide notice to Ionis that Otsuka wishes to share the costs of such Ionis [***] ("***Opt-In Notice***"). Following the receipt of an Opt-In Notice, Ionis shall provide an invoice to Otsuka for [***] of such Ionis [***] ("***Opt-In Fee***") as follows: [***]. Otsuka shall pay the Opt-In Fee within [***] after receipt of such invoice and supporting documentation; *provided* that, if Otsuka disputes any invoiced amount, then Otsuka will pay the undisputed invoiced amount within such [***] and will pay any disputed amounts within [***] following resolution of the dispute and determination that such amounts are owed. Following Otsuka's payment of the Opt-In Fee, (A) the Ionis [***] shall be deemed a Future Cross-Territory Study and will be added to the Cross-Territory Clinical Development Plan, (B) the Parties will share, [***], all Internal Costs reasonably incurred and External Costs incurred, in each case, directly by or on behalf of Ionis or its Affiliates in the performance of the Ionis [***] from the date on which Ionis provides a written report of the Ionis [***] Costs, (C) the applicable Ionis [***] shall be included within Ionis Know-How and subject to the licenses in Section 2.1 (License Grants to Otsuka), and (D) the Ionis [***] included in related Regulatory Submissions will be subject to Otsuka's right of use and right of reference provided in Section 5.9 (Right of Reference).]

4.5 **Development Reports**. At each JSC meeting, Ionis and Otsuka will each provide the JSC with a written summary of the activities conducted by or on behalf of such Party under, as applicable, the Cross-Territory Clinical Development Plan, the Non-Clinical HAE Development Plan, and the Otsuka Territory-Specific Development Plan, and with respect to Ionis, [***], in each case, since the last JSC meeting, including patient enrollment, the ongoing status, and material results of all Clinical Trials for the Licensed Products conducted by or on behalf of such Party. Each Party will also promptly provide written notice to the other Party and keep the other Party reasonably informed, through the JSC or Alliance Managers, of any significant Development events under the Cross-Territory Clinical Development Plan, the Non-Clinical HAE Development Plan, or the Otsuka Territory-Specific Development Plan, and with respect to Ionis, any additional Development activities conducted by or on behalf of Ionis or any of its Affiliates for the Licensed Product that are not set forth in the Cross-Territory Clinical Development Plan or the Non-Clinical HAE Development Plan, in each case, that [***] the Development activities of the other Party under this Agreement.

4.6 **Development Records; Cooperation**. Each Party and its Affiliates will maintain written or electronic records, in sufficient detail, in a good scientific manner, in accordance with Applicable Law (including GLP, GCP, and GMP, as applicable), and appropriate for regulatory and patent purposes, and that are complete and accurate and reflect all Development work performed and results achieved, in each case, by or on behalf of such Party and its Affiliates under, as applicable, the Cross-Territory Clinical Development Plan, the Non-Clinical HAE Development Plan, and the Otsuka Territory-Specific Development Plan, and with respect to Ionis, [***]. Each Party shall retain such records for at least three years after the end of the Term or for such longer period as may be required by Applicable Law. The Parties will cooperate with each other to achieve the Development objectives contemplated herein in a timely, accurate, and responsive manner. Without limiting the foregoing, [***].

4.7 **Data Transfer**. Upon Otsuka's reasonable request, Ionis shall provide to Otsuka, [***] notwithstanding the terms of Section 3.2 (Technology Transfer Cost), true and complete copies of all written, graphic or electronic embodiments of non-clinical data and clinical data generated by or on behalf of Ionis or any of its Affiliates in connection with the Development of Licensed Products, including all draft and final protocols and final study reports and raw data, in each case, to the extent such data is (a) Controlled by Ionis or its Affiliates and (b) [***] to Exploit a Licensed Product. [***].

ARTICLE 5
REGULATORY AFFAIRS

5.1 **Regulatory Responsible Party**. Ionis will be the Regulatory Responsible Party for the Licensed Products in the Ionis Territory. Otsuka will be the Regulatory Responsible Party for the Licensed Products in the Otsuka Territory, *provided* that, Ionis shall have the right to conduct regulatory activities in the Otsuka Territory, including interacting with Regulatory Authorities, solely with respect to (a) the Development activities for the Licensed Products in the Otsuka Territory for which Ionis is responsible under the Cross-Territory Clinical Development Plan and the Non-Clinical HAE Development Plan and (b) the Manufacturing activities for the Licensed Products for which Ionis is responsible in accordance with Article 7 (Manufacturing), in each case subject to the remainder of this Article 5 (Regulatory Affairs) ("***Ionis Regulatory Activities***"). Subject to the obligations in this Article 5 (Regulatory Affairs), the Regulatory Responsible Party will be responsible for, and [***] all Regulatory Submissions, communications, and other dealings with the Regulatory Authorities relating to the Licensed Products in the applicable Territory, and for seeking and maintaining all Regulatory Approvals with respect to the Licensed Product in the applicable Territory. The Regulatory Responsible Party will not be required to delay any submission, correspondence, or communication with any Regulatory Authorities in a manner that affects such Regulatory Responsible Party's ability to comply with any Regulatory Authority requirement or deadline or Applicable Law in such jurisdiction. For clarity, Otsuka or its designee shall be the holder of all Regulatory Approvals for the Licensed Product in the Otsuka Territory and will own all Regulatory Submissions in the Otsuka Territory, and Ionis or its designee shall be the holder of all Regulatory Approvals for the Licensed Product in the Ionis Territory and will own all Regulatory Submissions in the Ionis Territory. Otsuka will only [***] and will not [***].

5.2 **Regulatory Subcommittee**. Within [***] after the Effective Date, the Parties will establish, through the JSC, a Subcommittee to (a) oversee the preparation and submission of any MAA for a Licensed Product in the Otsuka Territory and (b) coordinate the regulatory responsibilities between the Parties in the Otsuka Territory, which allocation will be consistent with this Article 5 (Regulatory Affairs) (such Subcommittee, the "***Regulatory Subcommittee***"). The Regulatory Subcommittee will review and comment on any proposed MAA application for a Licensed Product sufficiently in advance of the filing or submission thereof by Otsuka, and Otsuka will [***] any comments received from the Regulatory Subcommittee. The Regulatory Subcommittee will meet as often as necessary to carry out the activities described in this Section 5.2 (Regulatory Subcommittee) and the terms of Section 8.2 (Additional Committees) will apply to the Regulatory Subcommittee.

5.3 **Correspondences with Regulatory Authorities**. Otsuka shall be solely responsible for communications with Regulatory Authorities in the Otsuka Territory regarding the Licensed Product and in no event will [***] regarding the Licensed Product in the Otsuka Territory, except in connection with [***], and subject to the remainder of this Section 5.3 (Correspondences with Regulatory Authorities). Ionis will [***]. In addition, Ionis will [***]. Furthermore, upon Otsuka's reasonable request and at [***], Ionis will [***]. The Regulatory Responsible Party will provide the other Party with (a) copies of any material written correspondence submitted to or received from (i) with respect to Otsuka, the EMA or any other Regulatory Authority in the Otsuka Territory, and (ii) with respect to Ionis, the FDA or any other Regulatory Authority in the U.S., and (b) summaries of any material oral communications with such Regulatory Authority in clause (a), in each case ((a) and (b)), relating to Regulatory Submissions in support of Development of the Licensed Products in such jurisdiction or country, reasonably promptly after receipt or delivery by such Regulatory Responsible Party of such correspondence or communication, as the case may be (but in any event, no later than [***] after receipt or delivery).

5.4 **Regulatory Meetings**. Ionis will [***] meetings pertaining to Regulatory Submissions for the Licensed Products relating to the Ionis Regulatory Activities [***] in the Otsuka Territory] to the extent not prohibited by Applicable Law or the applicable Regulatory Authority. At Otsuka's request, Ionis will [***]. With respect to all other meetings with any Regulatory Authority in the Otsuka Territory in support of Development of the Licensed Products, (a) Ionis will have the right, but not the obligation, [***] to attend such meetings [***] and (b) at Otsuka's reasonable request, Ionis will [***] and Otsuka will [***]. Further, Ionis will [***], unless Ionis reasonably believes that [***], and will not [***] except as (a) required by Applicable Law, (b) permitted pursuant to Section 12.4.1(b) (Permitted Circumstances) or Section 12.4.1(c) (Permitted Circumstances), or (c) authorized by Otsuka in writing. For clarity, the terms of this Section 5.4 (Regulatory Meetings) will apply solely with respect to any meetings with any Regulatory Authority in the Otsuka Territory in support of Development of the Licensed Products and do not apply to any meetings with Regulatory Authorities in the Otsuka Territory pertaining to [***].

5.5 **Regulatory Submissions**. Each Party (the "***Filing Party***") will provide the other Party with a copy of [***] (including, [***]) that the Filing Party intends to file with or submit to any Regulatory Authority in support of Development in the Otsuka Territory for the other Party's review and comment sufficiently in advance of the Filing Party's filing or submission thereof. The Filing Party will [***] any reasonable comments received from the other Party into such Regulatory Submissions. In addition and notwithstanding Section 3.2 (Technology Transfer Cost), Ionis will provide to Otsuka, [***].

5.6 **Cooperation**. The Parties will cooperate with each other to achieve the regulatory objectives contemplated herein in a timely, accurate, and responsive manner. Without limiting the foregoing or the terms of Section 5.5 (Regulatory Submissions), at Otsuka's reasonable request, Ionis will [***] of the Licensed Products in the Otsuka Territory or for obtaining and maintaining Regulatory Approval of the Licensed Products in the Otsuka Territory. If Otsuka receives any inquiry from a Regulatory Authority in the Otsuka Territory pertaining to any activities for which Ionis is responsible hereunder (including Cross-Territory Clinical Studies, non-clinical or CMC Development or Manufacturing (prior to the Manufacturing Handover Date)), then notwithstanding Section 3.2 (Technology Transfer Cost), upon Otsuka's request, Ionis will, [***]. In addition, upon Otsuka's reasonable request, Ionis shall provide [***] in the Otsuka Territory ("***Regulatory Support***"). Ionis will provide all Regulatory Support [***] until [***]. Thereafter, [***], Ionis will [***], and [***], Ionis will [***]. At all times, Otsuka will [***]. Ionis may [***] (i) [***], and (ii) [***] and, in each case ((i) and (ii)), [***] (and, with respect to [***]) therefor [***]. For clarity, if Otsuka requests Regulatory Support in connection with [***], Ionis shall provide such Regulatory Support [***], and Otsuka [***]. Notwithstanding any provision to the contrary, this Section 5.6 (Cooperation) will not require Ionis to conduct any additional Clinical Trials or generate any additional data or information that is not expressly contemplated by the Cross-Territory Clinical Development Plan or Non-Clinical HAE Development Plan.

5.7 **Cost of Regulatory Activities**. Except to the extent specified otherwise in this Article 5 (Regulatory Affairs), each Party will be responsible for all costs and expenses incurred in connection with its activities under this Article 5 (Regulatory Affairs), including the preparation or maintenance of Regulatory Submissions and Regulatory Approvals with respect to the Licensed Products for which it is responsible, including any filing fees and, with respect to Ionis, including all costs and expenses of Ionis Regulatory Activities and all costs and expenses related to the ASMF (if filed) and other regulatory affairs related to Manufacturing of Licensed Products, which in each case will be borne solely by Ionis.

5.8 **No Harmful Actions**. If [***], then such first Party will have the right to bring such matter to the attention of the JSC and the Parties will discuss in good faith to resolve such concern. Without limiting the foregoing and notwithstanding any provision to the contrary in this Agreement, Otsuka will not [***].

5.9 **Right of Reference**. Subject to the rules of the relevant Regulatory Authority and the terms of this Agreement, including Section 4.4.4(b) ([***] by Ionis), each Party hereby grants to the other Party a "Right of Reference," as that term is defined in 21 C.F.R. § 314.3(b) (or any successor rule or analogous Applicable Law recognized outside of the United States) to, and a right to copy, access, and otherwise use, all information and data relating to the Licensed Products in any Regulatory Submission or Regulatory Approval Controlled by the grantor Party during the Term (including, with respect to the grant to Otsuka, a right of reference to Ionis' Drug Master File and ASMF, if filed), solely for the other Party's or its Affiliates' use in the Development or Commercialization of the Licensed Products in the other Party's Territory in accordance with this Agreement. All such information and data contained in any such Regulatory Submissions or Regulatory Approvals will be considered Confidential Information of the grantor Party and subject to the terms of Article 12 (Confidentiality). If requested by the grantee Party, the grantor Party will provide a signed statement to this effect in accordance with 21 C.F.R. § 314.50(g)(3) (or any successor rule or analogous Applicable Law outside of the United States) to give effect to the intent of this Section 5.9 (Right of Reference).

5.10 **Pharmacovigilance; Safety Information**. Each Party will cooperate with the other Party, at no cost to the other Party (notwithstanding Section 3.2 (Technology Transfer Cost)), with regard to the reporting and handling of safety information involving the Licensed Products in accordance with Applicable Law, regulatory requirements, and regulations on pharmacovigilance and clinical safety. Otsuka will be responsible for all processing of information related to any adverse events for the Licensed Products in the Otsuka Territory and Ionis will be responsible for all processing of information related to any adverse events for the Licensed Products in the Ionis Territory, in each case, including any information regarding such adverse events that is received from a Third Party. Each Party will provide to the other Party in a timely manner the relevant safety information it receives (either directly or indirectly) related to the Licensed Products. At an appropriate time as agreed upon by the Parties following the Effective Date, but in any event prior to the [***], the Parties will negotiate in good faith and enter into a Pharmacovigilance Agreement related to the Licensed Products, which will define the pharmacovigilance responsibilities of the Parties and include safety data exchange procedures governing the exchange of information affecting the class and products (*e.g.*, Serious Adverse Events, emerging safety issues) to enable each Party to comply with all of its legal and regulatory obligations related to such Licensed Product. Prior to the execution of the Pharmacovigilance Agreement, each Party will have the right, upon reasonable notice to the other Party, to [***]. Ionis will own and maintain the global safety database for the Licensed Products at [***], *provided* that at Otsuka's reasonable request, Ionis will run queries of such global safety database and will provide copies of the data contained in such global safety database to the extent necessary or reasonably useful to the Development and Commercialization of the Licensed Product in the Otsuka Territory. As part of the negotiation of the Pharmacovigilance Agreement, the Parties will [***], taking into account that Ionis will own and maintain the global safety database, and the Parties' determination of such matter will be set forth in the Pharmacovigilance Agreement. Subject to compliance with Applicable Law, each Party hereby agrees to comply with its respective obligations under the Pharmacovigilance Agreement as the Parties may agree to modify it from time to time, and to cause its (sub)licensees to comply with such obligations. If there is a conflict between the terms and conditions of this Agreement and any terms and conditions of the Pharmacovigilance Agreement, then the terms and conditions of the Pharmacovigilance Agreement will govern with respect to any pharmacovigilance matters and this Agreement will govern with respect to any other matters.

5.11 **Pharmacovigilance Subcommittee**. The JSC shall establish a joint pharmacovigilance subcommittee (the "***PV Subcommittee***") at an appropriate time, but in any event prior to the [***]. In addition to any other matters that the JSC may delegate to the PV Subcommittee, the PV Subcommittee shall provide a forum for the Parties to discuss, share information, and escalate and attempt to resolve safety issues regarding the Licensed Product, and any other pharmacovigilance matters, worldwide. The PV Subcommittee will meet as often as necessary to carry out such activities, and the terms of Section 8.2 (Additional Committees) will apply to the PV Subcommittee.

5.12 **Ionis Internal Oligonucleotide Safety Database**.

5.12.1 Ionis maintains an internal database that includes information regarding the tolerability of its drug compounds, individually and as a class, including information discovered during non-clinical and clinical Development (the "***Ionis Internal Oligonucleotide Safety Database***"). To maximize understanding of the safety profile and pharmacokinetics of Ionis compounds, (a) Ionis will have the right to use any safety-related information provided by Otsuka pursuant to the Pharmacovigilance Agreement or this Section 5.12 (Ionis Internal Oligonucleotide Safety Database) to maintain the Ionis Internal Oligonucleotide Safety Database and (b) Otsuka will cooperate, at no cost to Ionis, with Ionis' reasonable requests in connection with populating the Ionis Internal Oligonucleotide Safety Database, including by providing Ionis with reasonably requested safety-related supporting data and answering any follow-up questions reasonably requested by Ionis or its Affiliates in connection with any information provided under the Pharmacovigilance Agreement, in each case to the extent such data and answers are reasonably available to Otsuka. In addition, with respect to Clinical Trials of the Licensed Products conducted by or on behalf of Otsuka pursuant to the Otsuka Territory-Specific Development Plan (if any), Otsuka will provide Ionis with copies of annual safety updates filed with each IND and the safety sections of any final Clinical Trial reports within [***] following the date such information is filed, as applicable. All such information disclosed by Otsuka to Ionis will be Otsuka Confidential Information; *provided*, *however*, that so long as Ionis does not disclose the identity of a Licensed Product or Otsuka's identity, Ionis may disclose any such Otsuka Confidential Information to (i) Ionis' other partners if such information is regarding class generic properties of oligonucleotides, (ii) any Third Party that contributes to the populating of the Ionis Internal Oligonucleotide Safety Database, or (iii) any Regulatory Authority. Otsuka will also cause its Affiliates and Sublicensees to comply with this Section 5.12 (Ionis Internal Oligonucleotide Safety Database).

5.12.2 From time to time, Ionis utilizes the information in the Ionis Internal Oligonucleotide Safety Database to conduct analyses to keep Ionis and its partners informed regarding class generic properties of oligonucleotides, including with respect to safety. As such, if and when Ionis identifies safety or other related issues that may be relevant to a Licensed Product (including any potential class-related toxicity), Ionis will promptly inform Otsuka of such issues and provide the data supporting Ionis' conclusions.

5.13 Recall, Withdrawal, or Field Alerts.

5.13.1 **Notification and Determination**. Each Party will notify the other Party immediately, and promptly confirm such notice in writing, if it obtains information indicating that any Licensed Product may be subject to a recall (whether voluntary or mandated), corrective action, or similar regulatory action by any Governmental Authority or Regulatory Authority (a "***Remedial Action***"). The Parties will assist each other in gathering and evaluating such information as is necessary to determine the necessity of conducting a Remedial Action with respect to the applicable Territory, and otherwise reasonably cooperate with each other with respect to such Remedial Action or potential Remedial Action. Ionis will have sole discretion and final decision-making authority with respect to, and control over, any Remedial Action in the Ionis Territory, including any decision to commence such Remedial Action in the Ionis Territory. Otsuka will have sole discretion and final decision-making authority with respect to, and control over, any Remedial Action in the Otsuka Territory, including any decision to commence such Remedial Action in the Otsuka Territory; *provided that* if Ionis notifies Otsuka of [***] that Ionis reasonably believes could give rise to a Remedial Action, then Otsuka will initiate such Remedial Action in accordance with Ionis' request and at [***].

5.13.2 **Cost Allocation**. Except as otherwise set forth in Section 5.13.1 (Notification and Determination), all costs directly associated with implementing a Remedial Action with respect to a Licensed Product will be allocated between Ionis and Otsuka as follows:

(a) If, and to the extent, that the Remedial Action arises as a result of [***], then [***] will bear all such costs and expenses; and

(b) in all other cases, Ionis will be responsible for such costs and expenses for such Licensed Product in the Ionis Territory and Otsuka will be responsible for such costs and expenses for such Licensed Product in the Otsuka Territory.

ARTICLE 6
COMMERCIALIZATION AND MEDICAL AFFAIRS

6.1 Commercialization Responsibilities for Licensed Product.

6.1.1 **Commercialization in the Ionis Territory**. Subject to the last sentence of Section 6.4 (Global Brand Strategic and Operating Plan) and the last sentence of Section 6.7.1 (Global Medical Affairs Plan), and without limiting Ionis' obligations under this Article 6 (Commercialization and Medical Affairs), Ionis and its Affiliates will have [***] with respect to the Commercialization of the Licensed Products in the Ionis Territory, including, if applicable, [***].

6.1.2 **Commercialization in the Otsuka Territory**. Subject to the terms and conditions of this Agreement, and without limiting Otsuka's obligations under this Article 6 (Commercialization and Medical Affairs), Otsuka and its Affiliates will have [***] with respect to the Commercialization of the Licensed Products in the Otsuka Territory, including [***]. Upon Otsuka's reasonable request, Ionis shall [***], including [***], and Ionis will [***].

6.1.3 **Coordination of Commercialization Activities**. The Parties will coordinate global Commercialization activities with respect to Commercialization of the Licensed Products in each Party's Territory through the JSC, as further set forth in Section 8.1 (Joint Steering Committee) and this Article 6 (Commercialization and Medical Affairs).

6.2 Commercialization and Medical Affairs Reporting. At each JSC meeting following the first Regulatory Approval for a Licensed Product in the Otsuka Territory, Otsuka will provide to the JSC a high-level summary (which may be in the form of a slide presentation) of the material Commercialization and Medical Affairs activities conducted by Otsuka or its Affiliates or Sublicensees for the Licensed Products in the Otsuka Territory during the period since the last JSC meeting and the material Commercialization and Medical Affairs activities expected to be conducted by Otsuka or its Affiliates, or Sublicensees in the Otsuka Territory for the Licensed Products during the period from the date of such update until the next JSC meeting, and shall answer any reasonable questions asked by Ionis to enable Ionis to assess Otsuka's compliance with its Commercialization diligence obligations set forth in Section 6.6 (Otsuka Commercialization Diligence Obligations). In addition, no later than [***], Otsuka will provide to the JSC a report of the forecasted Net Sales anticipated to be generated by Otsuka or its Affiliates, licensees, or Sublicensees in the Otsuka Territory during the upcoming Calendar Year, which forecast will be broken down on a country-by-country basis. At each JSC meeting following the first Regulatory Approval for a Licensed Product in the Ionis Territory, Ionis will provide to the JSC a high-level summary (which may be in the form of a slide presentation) of the material Commercialization and Medical Affairs activities conducted by Ionis or its Affiliates for the Licensed Products in the Ionis Territory during the period since the last JSC meeting and the material Commercialization and Medical Affairs activities expected to be conducted by Ionis or its Affiliates in the Ionis Territory for the Licensed Products during the period from the date of such update until the next JSC meeting. Without limiting the foregoing, at Otsuka's reasonable request, Ionis will provide to Otsuka, [***], all information relating to the [***].

6.3 **Pricing**. All decisions for the Licensed Products related to list price, targeted net pricing, sales-weighted average discounts and rebates, pricing strategy (including the approach to pricing with different types of accounts and plans, including types of discounts and rebates), and modifications to any of the foregoing, will be made by (a) Ionis in the Ionis Territory and (b) Otsuka in the Otsuka Territory; *provided* that, [***].

6.4 **Global Brand Strategic and Operating Plan**. Ionis will develop, [***] a global brand strategic and operating plan with respect to the Commercialization of the Licensed Products throughout the Territory (the "***Global Brand Strategic and Operating Plan***"). The Global Brand Strategic and Operating Plan shall at all times conform to applicable Professional Requirements and Applicable Law (including compliance requirements). Ionis, through the JSC, will update the Global Brand Strategic and Operating Plan [***]. In addition, [***], either Party may propose material updates or modifications to the Global Brand Strategic and Operating Plan to [***]. No update or modification to the Global Brand Strategic and Operating Plan will be effective unless and until [***]. Once [***], such updated version of the Global Brand Strategic and Operating Plan will automatically become effective and replace the then-prior version of the Global Brand Strategic and Operating Plan. The Global Brand Strategic and Operating Plan will include, in reasonable detail, the Trademarks to be used by the Parties or its Affiliates or its or their Sublicensees for the Commercialization of Licensed Product, trade dress, positioning, market access strategy, and marketing strategic imperatives, objectives and messaging with respect to the Licensed Products. At Otsuka's reasonable request, Ionis will provide to Otsuka, [***]. Ionis will, [***], lead and conduct all Commercialization activities for the Licensed Products in the Ionis Territory [***].

6.5 **Otsuka Territory Brand Strategic and Operating Plan**. Within [***] after [***] approves the initial Global Brand Strategic and Operating Plan, Otsuka will prepare and submit to [***] a brand strategic and operating plan with respect to the Commercialization of the Licensed Products in the Otsuka Territory (such plan, the "***Otsuka Territory Brand Strategic and Operating Plan***"). [***] will review, discuss and determine whether to approve the initial Otsuka Territory Brand Strategic and Operating Plan. The Otsuka Territory Brand Strategic and Operating Plan will, at all times during the Term, be consistent with the then-current Global Brand Strategic and Operating Plan, except to the extent such inconsistency is (a) necessary to (i) conform with any written requirement from any Regulatory Authority or with any Applicable Law or Professional Requirements in the Otsuka Territory or (ii) avoid infringement of a Third Party Trademark in the Otsuka Territory, or (b) approved by the JSC (by unanimous Party Vote). On [[***] during the Term (and more frequently as may be necessary), Otsuka will prepare an update to the Otsuka Territory Brand Strategic and Operating Plan. [***] will review, discuss and determine whether to approve each update to the Otsuka Territory Brand Strategic and Operating Plan. Once approved by [***], the Otsuka Territory Brand Strategic and Operating Plan will automatically become effective and, in the case of an update, will supersede the previous Otsuka Territory Brand Strategic and Operating Plan as of the date of such approval by [***]. Otsuka will, at its cost and expense, lead and conduct all Commercialization activities in the Otsuka Territory [***].

6.6 **Otsuka Commercialization Diligence Obligations**. On a country-by-country basis in the Otsuka Territory, following [***], Otsuka will use Commercially Reasonable Efforts to obtain Reimbursement Approval for and otherwise Commercialize such Licensed Product in such country.

6.7 **Medical Affairs Plans**.

6.7.1 **Global Medical Affairs Plan**. Ionis will develop, and will [***], a plan for the global Medical Affairs activities for the Licensed Products throughout the Territory (the "***Global Medical Affairs Plan***"). The Global Medical Affairs Plan shall at all times conform to applicable Professional Requirements and Applicable Law (including compliance requirements) with adjustments necessary to comply with local Applicable Law and Professional Requirements in the Otsuka Territory. Ionis, through the JSC, will update the Global Medical Affairs Plan on [***] basis. In addition, between [***] updates, either Party may propose material updates or modifications to the Global Medical Affairs Plan [***]. No update or modification to the Global Medical Affairs Plan will be effective unless and until approved by [***]. Once approved by [***], such updated version of the Global Medical Affairs Plan will become effective and replace the then-prior version of the Global Medical Affairs Plan. Ionis will, at its cost and expense, lead and conduct all Medical Affairs activities for the Licensed Products in the Ionis Territory [***].

6.7.2 **Otsuka Territory Medical Affairs Plan**. Within [***] after [***] approves the initial Global Medical Affairs Plan, Otsuka will prepare and submit to [***] a plan for the Medical Affairs activities for the Licensed Products in the Otsuka Territory (such plan, the "***Otsuka Territory Medical Affairs Plan***"). [***] will review, discuss and determine whether to approve the initial Otsuka Territory Medical Affairs Plan. The Otsuka Territory Medical Affairs Plan will, at all times during the Term, be consistent with the then-current Global Medical Affairs Plan, except to the extent such inconsistency is (a) necessary to conform with any written requirement from any Regulatory Authority or with any Applicable Law or Professional Requirements in the Otsuka Territory or (b) approved by the JSC (by unanimous Party Vote). On [***] during the Term (and more frequently as may be necessary), Otsuka will prepare an update to the Otsuka Territory Medical Affairs Plan. [***] will review, discuss, and determine whether to approve each update to the Otsuka Territory Medical Affairs Plan. Once approved by [***], the Otsuka Territory Medical Affairs Plan will automatically become effective and, in the case of an update, supersede the previous Otsuka Territory Medical Affairs Plan as of the date of such approval by the JSC. Otsuka will, at its cost and expense, lead and conduct all Medical Affairs activities in the Otsuka Territory [***].

6.8 Standards of Conduct; Compliance. Each Party will perform, or will ensure that each of its Affiliates, Sublicensees, and Subcontractors perform, all Commercialization and Medical Affairs activities in a professional and ethical business manner and in compliance with Applicable Law and applicable Professional Requirements.

6.9 Product Materials. Each Party will, at its cost and expense, be responsible for preparing, developing, producing, or otherwise obtaining, and utilizing promotional materials, training materials, medical education materials, Packaging and Labeling, and all other literature or other information related to the Licensed Products ("***Product Materials***") to support its Commercialization and Medical Affairs activities in such Party's Territory, which Product Materials will at all times [***]. From time to time, and in any event upon Otsuka's request, Ionis will share with Otsuka samples of Product Materials Controlled by Ionis and which are used by Ionis, its Affiliates, or licensees in connection with the Commercialization of or conduct of Medical Affairs activities for the Licensed Products. From time to time, and in any event upon Ionis' request, Otsuka will share with Ionis samples of Product Materials Controlled by Otsuka and which are used by Otsuka, its Affiliates or sublicensees in connection with the Commercialization of or conduct of Medical Affairs activities the Licensed Products in the Otsuka Territory.

6.10 Diversion. Neither Party nor its Affiliates will, and each Party will take reasonable measures to ensure that its Sublicensees, licensees, and Subcontractors do not, either directly or to such Party's knowledge, intentionally indirectly, promote, market, distribute, import, sell, or have sold any Licensed Product to any Third Party or to any address or Internet Protocol address or the like outside of such Party's Territory including via the Internet or mail order. Notwithstanding any provision to the contrary set forth in this Agreement, [***]. As applicable, (i) in the case of Otsuka, in any country or jurisdiction outside of the Otsuka Territory, and (ii) in the case of Ionis, in any country or jurisdiction outside of the Ionis Territory:

6.10.1 such Party and its Affiliates will not engage, nor permit its Sublicensees, licensees, and Subcontractors to engage, in any advertising or promotional activities relating to any Licensed Product for use directed primarily to customers or other buyers or users of the Licensed Products located in any such country or jurisdiction;

6.10.2 such Party and its Affiliates will not solicit orders of the Licensed Products from any prospective purchaser located in any such country or jurisdiction;

6.10.3 such Party and its Affiliates will not, and will take reasonable measures to cause its Sublicensees, licensees and Subcontractors to not, deliver or tender (or cause to be delivered or tendered) any Licensed Product to Third Parties for use in such country or jurisdiction; and

6.10.4 if either Party or its Affiliates, Sublicensees, or licensees receive any order for any Licensed Product from a prospective purchaser located in any such country or jurisdiction, then such Party will immediately refer that order to the other Party or its designee and will not accept any such orders.

ARTICLE 7
MANUFACTURING

7.1 Responsibility.

7.1.1 **Ionis Manufacturing**. Ionis will have sole control over and decision-making authority with respect to, at its cost and expense, the Manufacture of (a) all supplies of the Licensed Products required for Ionis' activities under the Cross-Territory Clinical Development Plan and the Non-Clinical HAE Development Plan, and for all Development activities in the Ionis Territory and (b) all supplies of the Licensed Products for Commercialization purposes in the Ionis Territory. In addition, but subject to Section 7.1.2 (Otsuka Manufacturing), in accordance with the Supply Agreements and Quality Agreements, Ionis will Manufacture and supply Otsuka with all Licensed Product that is necessary for Otsuka to (i) [***] and (ii) [***]. Upon Otsuka's reasonable request prior to the Manufacturing Handover Date, Ionis will provide (or will use commercially reasonable efforts to cause its CMOs to provide) to Otsuka (A) [***], (B) [***], and (C) [***]. Ionis will provide all such Requested Assistance to Otsuka in accordance with the terms of Section 3.2 (Technology Transfer Cost) and will provide such data and information to Otsuka [***]. For clarity, and notwithstanding anything to the contrary herein, Ionis will provide to the Qualified Person for the Licensed Products in the Otsuka Territory, [***], Manufacturing audit or inspection reports as required under EU GMP, Annex 16, section 2.2 for the purposes of batch certification in the Otsuka Territory.

7.1.2 **Otsuka Manufacturing**. Otsuka will have the right to assume responsibility for Manufacturing (a) all supplies of the Licensed Products required for Otsuka's activities under the Otsuka Territory-Specific Development Plan and (b) all supplies of the Licensed Products for Commercialization purposes in the Otsuka Territory, in each case, upon written notice to Ionis at any time after the earliest of (i) [***], (ii) [***] and (iii) [***] (such notice, a "***Manufacturing Handover Notice***"). If Otsuka provides Ionis with a Manufacturing Handover Notice, then Ionis' obligations to Manufacture and supply Otsuka in accordance with Section 7.1.1 (Ionis Manufacturing) will terminate, following the completion of all activities under the Manufacturing Technology Transfer Agreement in accordance with Section 7.4 (Manufacturing Technology Transfer), and the initiation of actual Manufacturing of the Licensed Products to be sold by or on behalf of Otsuka at Otsuka's or its designee's manufacturing facility (such date, the "***Manufacturing Handover Date***").

7.2 Supply and Quality Agreements; Manufacturing Costs.

7.2.1 **Clinical Supply Agreement**. Unless otherwise agreed by the Parties, within a timeframe following the Effective Date to be agreed by the Parties, the Parties will negotiate in good faith and enter into a supply agreement on reasonable and customary terms for the supply of Licensed Products by Ionis to Otsuka for clinical use (the "***Clinical Supply Agreement***"), which agreement (together with the related Quality Agreement) will govern the terms and conditions of the Manufacture and supply of the Licensed Products for Development purposes in the Otsuka Territory. Otsuka will pay a supply price to Ionis under the Clinical Supply Agreement equal to [***].

7.2.2 **Commercial Supply Agreement**. Within a timeframe following the Effective Date to be agreed by the Parties, the Parties will negotiate in good faith and enter into a commercial supply agreement on reasonable and customary terms for the commercial-grade supply of Licensed Products by Ionis to Otsuka (the "***Commercial Supply Agreement***" and together with the Clinical Supply Agreement, the "***Supply Agreements***"), which agreement (together with the related Quality Agreement) will govern the terms and conditions of the Manufacture and supply of the Licensed Products for Commercialization purposes in the Otsuka Territory. Otsuka will pay a supply price to Ionis under the Commercial Supply Agreement equal to [***]. The Commercial Supply Agreement shall allow Otsuka to order, and Ionis to supply, a portion of a batch as minimum order quantity, for a duration of at least [***], as further detailed in such Commercial Supply Agreement.

7.2.3 **Quality Agreements**. The Parties will negotiate in good faith and enter into one or more quality technical agreements pertaining to clinical and commercial supply of Licensed Products to Otsuka (each, a "***Quality Agreement***") containing reasonable and customary terms and conditions regarding quality assurance, quality control, compliance with GMP, GDP and GCP (as applicable), specifications, change control procedures, and provisions relating to audits and inspections.

7.2.4 **Manufacturing Cost Increases**. If the Manufacturing Costs, whether for clinical or commercial supplies of Licensed Product, are reasonably anticipated to increase, on a per unit basis, such that the [***], then Ionis will provide prompt written notice to Otsuka of such increase. If such increase is anticipated to result in [***], on a per unit basis, then [***]. If such increase is anticipated to result in [***] on a per unit basis, then [***].

7.2.5 **Capital Expenditures**. Ionis [***]. In addition, if any CMO requests or requires [***], then Ionis will notify Otsuka and the Parties will [***].

7.2.6 [***]. If the reasonable allocation of [***], then [[***].

7.3 Audits and Inspections.

7.3.1 **By Otsuka**. Prior to execution of the first Quality Agreement, Otsuka shall be entitled to conduct [***]. In addition, if Ionis elects to inspect or audit any facilities of its CMOs with respect to the Manufacture of Licensed Products for the Otsuka Territory, Ionis shall notify Otsuka of such inspection or audit and, [***]. In addition, to the extent permitted under Ionis' agreement with the applicable CMO and subject to any conditions set forth in such agreement with respect to any inspection or audit (e.g., an obligation to enter into a confidentiality agreement with the applicable CMO), Ionis shall [***]. If Otsuka identifies the need to perform a "for cause" audit of such facilities to address quality or compliance issues related to any Licensed Product Manufactured for the Otsuka Territory (including to address any notice from a Governmental Authority in the Otsuka Territory of noncompliance with Applicable Laws), as well as in connection with the preparation of Regulatory Submissions for the Otsuka Territory and in response to Regulatory Authority requirements in the Otsuka Territory, then Otsuka shall notify Ionis and if Ionis agrees with Otsuka's determination that a "for cause" audit is needed, Ionis will schedule and conduct such audit and Otsuka will [***], in each case, to the extent permitted pursuant to the applicable agreement with the such CMO.

7.3.2 **By Governmental Authority**. If any Governmental Authority carries out or gives notice of its intention to carry out any inspection or audit of any of Ionis' CMOs in relation to Manufacture of Licensed Products for the Otsuka Territory and Ionis is aware of such upcoming inspection or audit, then Ionis shall promptly notify Otsuka thereof and Ionis shall, to the extent permitted by its agreement with the applicable CMO and the applicable Governmental Authority, [***]. Following receipt by Ionis of the inspection results or audit observations of the Governmental Authority from such inspection or audit (a redacted copy of which Ionis will promptly provide to Otsuka to the extent it relates to Licensed Products Manufactured for the Otsuka Territory), Ionis will (a) prepare any appropriate responses and (b) provide a copy of such responses to Otsuka [***] in advance of the date such responses are due, to the extent such responses pertain to the Manufacture of Licensed Products for the Otsuka Territory, and Ionis shall [***], in each case ((a) and (b)), to the extent permitted under Ionis' agreement with such CMOs and subject to any conditions set forth in the applicable agreement with such CMOs with respect to any inspection or audit (e.g., an obligation to enter into a confidentiality agreement with the applicable CMO).

7.3.3 **CMO Agreements**. Ionis shall [***].

7.4 Manufacturing Technology Transfer. At Otsuka's request any time after Otsuka provides a Manufacturing Handover Notice, Ionis will make available to Otsuka all Ionis Manufacturing and Analytical Know-How and materials (the "***Manufacturing Technology Transfer***"). Otsuka will (a) use Ionis Manufacturing and Analytical Know-How and materials provided by Ionis in connection with the Manufacturing Technology Transfer only in the fulfillment of obligations or exercise of rights under this Agreement, and (b) not transfer such Ionis Manufacturing and Analytical Know-How or materials or deliver the same to any Third Party, without Ionis' prior written consent. For purposes of the Manufacturing Technology Transfer, the Parties together with Ionis' CMO (subject to the next sentence) will enter into a manufacturing technology transfer agreement, which will also provide for reasonable technical assistance and support by Ionis and Ionis' CMOs as reasonably requested by Otsuka to enable Otsuka or its Affiliates, or if agreed by Ionis, a Third Party manufacturer (other than Ionis' CMOs), to Manufacture the Licensed Products ("***Manufacturing Technology Transfer Agreement***"). Ionis will use reasonable efforts to [***]. If Ionis agrees to transfer Ionis Manufacturing and Analytical Know-How to a Third Party manufacturer other than Ionis' CMOs, such transfer shall be carried out pursuant to a direct license between Ionis and such Third Party manufacturer. If Otsuka [***]. Otsuka will [***]. Accordingly, Ionis may [***]. Each Party will [***].

ARTICLE 8
GOVERNANCE

8.1 Joint Steering Committee.

8.1.1 **Formation and Purpose of the JSC**. Promptly, but not more than [***] after the Effective Date, Ionis and Otsuka will establish a Joint Steering Committee ("***JSC***"), which will have the responsibilities set forth in this Article 8 (Governance) and will oversee, review, monitor, coordinate, and, where specified in this Section 8.1 (Joint Steering Committee), approve the Parties' Development, Manufacturing, Medical Affairs, and Commercialization activities under this Agreement for the Licensed Products in the Territory in accordance with this Section 8.1 (Joint Steering Committee). The JSC will dissolve upon the expiration of the Term.

8.1.2 **Membership**. The JSC will be composed of an equal number of representatives from each Party who have the appropriate and direct knowledge and expertise and requisite decision-making authority. Any such representative who serves on the JSC or any committee under this Agreement may also serve on one or more other committees under this Agreement. Each Party may replace any of its representatives on the JSC and appoint a person to fill the vacancy arising from each such replacement. A Party that replaces a representative will notify the other Party at least [***] prior to the next scheduled meeting of the JSC. Ionis will designate one of its JSC members as one of the co-chairpersons of the JSC and Otsuka will designate one of its members as the other co-chairperson of the JSC (each, a "***JSC Co-Chairperson***"). The JSC Co-Chairpersons or their designees, in collaboration with the Alliance Managers, will be responsible for calling meetings, preparing and circulating an agenda and related information in advance of each meeting, and preparing and issuing minutes of each meeting within [***] thereafter. Such minutes will not be finalized until the JSC Co-Chairpersons or their designees have had [***] to review and confirm the accuracy of such minutes.

8.1.3 **Meetings**. The JSC will hold meetings at such times as it elects to do so, but will meet no less frequently than quarterly prior to [***] and thereafter no less frequently than [***], in each case, unless otherwise agreed by the Parties. The JSC may meet in person or by means of teleconference, Internet conference, video conference, or other similar communication method. Each Party will be responsible for all of its own costs and expenses of participating in any JSC meeting.

8.1.4 **Meeting Agendas**. Unless agreed otherwise by the Parties, the Parties will jointly prepare the agenda for each JSC meeting, facilitated by the Alliance Managers working closely with the JSC Co-Chairpersons and, as appropriate, other JSC members and Subcommittee co-chairpersons, at least [***] in advance of each meeting of the JSC, and each Party will provide the other Party with all relevant materials to be presented at each JSC meeting at least [***] in advance of each meeting of the JSC; *provided* that under exigent circumstances requiring JSC input, the agenda may be prepared or presentation materials may be provided within a shorter period of time in advance of a meeting, with the approval of the JSC Co-Chairpersons. Either Party may propose that there not be a specific agenda for a particular meeting, so long as the other Party consents to the later addition or modification of agenda items or the absence of a specific agenda for such JSC meeting.

8.1.5 **Specific Responsibilities of the JSC**. The responsibilities of the JSC will be to:

(a) manage the overall strategic alignment between the Parties under this Agreement and maintain the relationship between the Parties;

(b) review, discuss, and determine whether to [***];

(c) review, discuss, and determine whether [***];

(d) review, discuss, and determine whether [***];

(e) review, discuss, and determine whether [***];

(f) review, discuss and determine whether [***];

(g) review, discuss, and determine whether to approve any updates to the Shared Development Budget, as described in Section 4.4.2(a) (Shared Development Budget);

(h) review, discuss, and determine whether to approve [***] and the Shared Development Budget, as described in Section 4.4.4(a) (Shared Costs);

(i) share information related to, and review and discuss activities and progress of each Party in connection with the Development of Licensed Products in its Territory, including activities and progress under the Cross-Territory Clinical Development Plan, Non-Clinical HAE Development Plan, and the Otsuka Territory-Specific Development Plan, including through updates from each Party of the status of Development for the Licensed Products in each Party's Territory, as described in Section 4.5 (Development Reports);

(j) review and discuss any matters related to the Development of the Licensed Products referred to the JSC by either Party's representatives;

(k) discuss any concerns raised by either Party regarding any action that the other Party is taking or intends to take with respect to a Licensed Product that is [***], as described in Section 5.8 (No Harmful Actions);

(l) discuss [***];

(m) review, discuss, and determine whether to approve [***];

(n) review, discuss, and determine whether to approve [***];

(o) review, discuss, and determine whether to approve [***];

(p) review, discuss and determine whether to approve [***];

(q) review and discuss any matters related to the Commercialization of the Licensed Products referred to the JSC by either Party's representatives;

(r) discuss the inclusion of Ionis' logo, name, and housemark on the packaging for the Licensed Products in the Otsuka Territory, as described in Section 10.10.6 (Housemarks);

(s) establish and delegate specifically defined duties to any Subcommittees, as described in Section 8.2.1 (Formation; Authority);

(t) attempt to resolve any disputes or disagreements arising from matters within the jurisdiction of any Subcommittee; and

(u) perform such other functions as appropriate to further the purposes of this Agreement as determined by the Parties.

8.2 Additional Committees.

8.2.1 **Formation; Authority**. In addition to the Regulatory Subcommittee and the PV Subcommittee, the JSC may establish and delegate specifically-defined duties to operational committees or *ad hoc* subcommittees, on an "as needed" basis to oversee particular projects or activities (any such operational committees and subcommittees, including the Regulatory Subcommittee, a "***Subcommittee***"). Each such Subcommittee will be constituted and will operate as the JSC determines. Each Subcommittee and its activities will be subject to the oversight of, and will report to, the JSC. The JSC or the JSC Co-Chairpersons, in each case as mutually agreed, may delegate to a Subcommittee any responsibilities of the JSC set forth in Section 8.1.5 (Specific Responsibilities of the JSC), and, in such case, any agreement reached by unanimous Party Vote of the applicable Subcommittee with respect to such delegated responsibilities will be deemed to be approved by the JSC (to the extent such approval is required hereunder). The JSC or the JSC Co-Chairpersons acting together may also reallocate any responsibility of a Subcommittee to any other Subcommittee. No Subcommittee's authority may exceed that specified for the JSC in this Article 8 (Governance). Any disagreement between the representatives of the Parties on a Subcommittee will be referred to the JSC for resolution in accordance with Section 8.4 (Decision-Making).

8.2.2 **Subcommittee Leadership and Meetings**. Ionis will designate a co-chairperson of each Subcommittee and Otsuka will designate a co-chairperson of each Subcommittee, each of whom will be a Party's representative who is a member of such Subcommittee (each, a "***Subcommittee Co-Chairperson***"). The Subcommittee Co-Chairpersons or their designees, in collaboration with the Alliance Managers, will be responsible for calling meetings, preparing and circulating an agenda in advance of each meeting, and preparing and issuing minutes of each meeting promptly thereafter. Such minutes will not be finalized until all Subcommittee members have had [***] to review and confirm the accuracy of such minutes. Each Party may replace its representatives and Subcommittee Co-Chairpersons on each such Subcommittee at any time upon written notice to the other Party. The Alliance Manager of each Party (or his or her designee) will attend each meeting of each Subcommittee as a non-voting participant. Each Subcommittee will hold meetings at such times as it elects to do so, and at such locations as the Parties may agree upon or by means of teleconference, Internet conference, video conference, or other similar communication method. Each Party will be responsible for all of its own expenses of participating in any Subcommittee meeting.

8.3 **Additional Participants**. Employees of a Party or any of its Affiliates involved in the Exploitation of the Licensed Products may attend meetings of the JSC or any Subcommittee as non-voting participants. In addition, with the prior consent of each Party, consultants, representatives, or advisors involved in the same activities and under written obligations of confidentiality and non-use applicable to the Confidential Information of each Party that are at least as stringent as those set forth in Article 12 (Confidentiality) may attend meetings of the JSC or any Subcommittee as non-voting observers.

8.4 **Decision-Making**.

8.4.1 **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 may be reflected in the minutes of the committee meeting or by an action by written consent signed by the JSC Co-Chairpersons or their designees identified in writing. Except as otherwise expressly set forth in this Agreement, the phrase "determine," "designate," "approve," or "determine whether to approve" by the JSC or any Subcommittee and similar phrases used in this Agreement will mean approval in accordance with this Section 8.4 (Decision-Making), including the escalation and tie-breaking provisions herein. For the avoidance of doubt, matters that are specified in Section 8.1.5 (Specific Responsibilities of the JSC) to be reviewed and discussed (as opposed to reviewed, discussed, and approved) do not require any agreement or decision by either Party and are not subject to the voting and decision-making procedures set forth in this Section 8.4 (Decision-Making) or Section 8.5 (Resolution of Committee Disputes).

8.4.2 **Decisions of the Subcommittees**. If any Subcommittee cannot reach unanimous agreement using good faith efforts on any matter within their respective scope of authority within [***] of the meeting at which such matter was discussed, then a Party may refer such matter to the JSC for resolution in accordance with Section 8.4.3 (Decisions of the JSC).

8.4.3 **Decisions of the JSC**. The JSC will use good faith efforts, in compliance with this Section 8.4.3 (Decisions of the JSC), to promptly resolve any such matter for which it has authority. If, after the use of good faith efforts, including reasonable discussion and good faith consideration of each Party's view on a particular matter, the JSC is unable to resolve any such matter referred to it by any Subcommittee or any matter with respect to the matters within the scope of the JSC's authority, in each case, within a period of [***], then either Party may refer such matter to the Party's respective Executive Officer for resolution in accordance with Section 8.5.1 (Referral to Executive Officers).

8.5 **Resolution of Committee Disputes**.

8.5.1 **Referral to Executive Officers**. If a Party makes an election under Section 8.4.3 (Decisions of the JSC) to refer for resolution by the Executive Officers a matter as to which the JSC cannot reach a consensus decision, then the JSC will submit in writing the respective positions of the Parties to their respective Executive Officers. The Executive Officers will use good faith efforts to resolve any such matter so referred to them as soon as practicable but, in any event, within [***] after such matter is referred to them (or such longer period as the Executive Officers may agree upon), and any final decision that the Executive Officers agree to in writing will be conclusive and binding on the Parties.

8.5.2 **Final Decision-Making Authority**. If the Executive 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 Executive Officers may agree upon), then, subject to Section 8.5.3 (Limitations on Decision Making):

(a) **No Change; Status Quo**. Neither Party will have final decision-making authority with respect to the final resolution of any disagreement related to: (i) [***]; (ii) [***]; (iii) [***]; (iv) [***]; (v) [***]; and (vi) [***].

(b) **Ionis Final Decision-Making Authority**. Ionis will have final decision-making authority over (i) [***], (ii) [***], (iii) [***], (iv) [***], and (vi) [***]. Notwithstanding the foregoing, [***].

(c) **Otsuka Final Decision-Making Authority**. Otsuka will have final decision making authority over (i) [***], (ii) [***], (iii) [***], and (iv) [***].

8.5.3 **Limitations on Decision Making**. Notwithstanding anything to the contrary set forth in this Agreement, without the other Party's prior written consent, no decision of the JSC, any Subcommittee, or a Party's Executive Officer (in the exercise of a Party's decision-making authority on any such matters), in each case may, without the other Party's prior written consent, (a) be likely to [***], (b) impose any requirements that the other Party take or decline to take any action that a Party reasonably believes would result in a violation of any Applicable Law, the requirements of any Regulatory Authority, or any agreement with any Third Party (including any Collaboration In-License) or the infringement or misappropriation of intellectual property rights of any Third Party, or (c) conflict with, amend, interpret, modify, or waive compliance under this Agreement.

8.6 **Day-to-Day Responsibilities**. Each Party will: (a) be responsible for day-to-day implementation and conduct of the activities hereunder for which it has or is otherwise assigned responsibility under this Agreement, *provided* that such implementation is consistent with the express terms of this Agreement or the decisions of the JSC within the scope of its authority as provided herein; and (b) provide the other Party with information about material events related to the progress of such activities, as may be reasonably requested by the other Party from time to time.

8.7 **Alliance Managers**. Each of the Parties will appoint a representative of such Party to act as its alliance manager under this Agreement no later than [***] after the Effective Date (each, an "***Alliance Manager***"). The role of the Alliance Manager is to act as a single point of contact between the Parties to ensure a successful relationship under this Agreement. The Alliance Managers will attend all JSC meetings and the Alliance Managers or their respective designees will attend all Subcommittee meetings and will support the JSC Co-Chairpersons and any Subcommittee Co-Chairpersons in the discharge of their responsibilities. Alliance Managers will be non-voting participants in all JSC and Subcommittee meetings, but an Alliance Manager may bring any matter to the attention of the JSC or any Subcommittee if such Alliance Manager reasonably believes that such matter warrants such attention. Each Party may change its designated Alliance Manager at any time upon written notice to the other Party. Any Alliance Manager may designate a substitute to temporarily perform the functions of that Alliance Manager by written notice to the other Party. Each Alliance Manager will also: (a) be the point of first referral in all matters of conflict resolution; (b) provide a single point of communication for seeking consensus between the Parties regarding key strategy and plan issues; (c) identify and bring disputes to the attention of the JSC in a timely manner; (d) plan and coordinate cooperative efforts and internal and external communications; and (e) take responsibility for ensuring that governance activities, such as the conduct of required JSC and any Subcommittee meetings and production of meeting minutes, occur as set forth in this Agreement, and that the relevant action items resulting from such meetings are appropriately carried out or otherwise addressed.

ARTICLE 9
PAYMENTS

9.1 **Upfront Payment**. Following the Effective Date, within [***], Otsuka will pay to Ionis, by wire transfer of immediately available funds, a non-refundable, non-creditable upfront payment of $65,000,000 (the "***Upfront Payment***").

9.2 **Milestone Payments**.

9.2.1 **Regulatory Milestones**. Subject to Section 9.2.1(a) (Regulatory Milestone Adjustment), after the first achievement of each regulatory milestone event set forth in Table 9.2.1 below by Otsuka or its Affiliates or Sublicensees for the first Licensed Product, Otsuka will pay to Ionis the corresponding regulatory milestone payment set forth in Table 9.2.1 (the regulatory milestone events set forth in Table 9.2.1, the "***Regulatory Milestone Events***" and the regulatory milestone payments set forth in Table 9.2.1, the "***Regulatory Milestone Payments***").

Table 9.2.1 –Regulatory Milestones

	Regulatory Milestone Event	***Regulatory Milestone Payment (in U.S. Dollars)***
1.	[***]	$[***]
2.	[***]	$[***]
3.	[***]	$[***]

(a) **Regulatory Milestone Adjustment**. If any [***], then the Regulatory Milestone Payments will be [***].

(b) **Notice and Payment**. Otsuka will notify Ionis in writing of the achievement of each Regulatory Milestone Event within [***] after achievement of such Regulatory Milestone Event by Otsuka or its Affiliates or within [***] after Otsuka's receipt of notification of such achievement by its Sublicensees. However, in no event will a failure or delay by Otsuka to deliver such notice of achievement of a Regulatory Milestone Event relieve Otsuka of its obligation to pay Ionis the corresponding Regulatory Milestone Payment for achievement of such Regulatory Milestone Event. Following receipt of such notice, Ionis will send Otsuka an invoice (and, if there has been any change to a Payment Form previously submitted, or if a previously submitted Payment Form has expired, then an updated Payment Form) for the applicable Regulatory Milestone Payment, and Otsuka shall pay such Regulatory Milestone Payment within [***] after receipt of such invoice (and Payment Forms, if applicable). Each Regulatory Milestone Payment is payable only once, regardless of the number of times the corresponding Regulatory Milestone Event is achieved. If Otsuka or its Affiliates or Sublicensees achieve all of the Regulatory Milestone Events, then the Regulatory Milestone Payments payable by Otsuka under this Section 9.2.1 (Regulatory Milestones) will not exceed $[***].

9.2.2 **Sales Milestones**. After each sales milestone event set forth in Table 9.2.2 below is achieved by Otsuka or its Affiliates or Sublicensees for the Licensed Products in the Otsuka Territory, Otsuka will pay to Ionis the corresponding sales milestone payment, as set forth below (the sales milestone events set forth in Table 9.2.2, the "***Sales Milestone Events***" and the sales milestone payments set forth in Table 9.2.2, the "***Sales Milestone Payments***").

Table 9.2.2 – Sales Milestones	
Sales Milestone Event	***Sales Milestone Payment (in U.S. Dollars)***
First Calendar Year in which the aggregate annual Net Sales of the Licensed Products in the Otsuka Territory equal or exceed [***]	$[***]
First Calendar Year in which the aggregate annual Net Sales of the Licensed Products in the Otsuka Territory equal or exceed [***]	$[***]
First Calendar Year in which the aggregate annual Net Sales of the Licensed Products in the Otsuka Territory equal or exceed [***]	$[***]

(a) **Notice and Payment**. Otsuka will notify Ionis in writing of the achievement of each Sales Milestone Event no later than (i) [***] or (ii) [***]. However, in no event will a failure or delay by Otsuka to deliver such notice of achievement of a Sales Milestone Event relieve Otsuka of its obligation to pay Ionis the corresponding Sales Milestone Payment for achievement of such Sale Milestone Event. Following receipt of such notice, Ionis will send Otsuka an invoice (and, if there has been any change to a Payment Form previously submitted, or if a previously submitted Payment Form has expired, then an updated Payment Form) for the applicable Sales Milestone Payment, and Otsuka shall pay such Sales Milestone Payment within [***] after receipt of such invoice (and Payment Forms, if applicable). If more than one of the Sales Milestone Events is achieved for the first time in a given Calendar Quarter during the Term, then Otsuka will pay to Ionis a separate Sales Milestone Payment with respect to each such Sales Milestone Event. Each Sales Milestone Payment is payable only once, regardless of the number of times the corresponding Sales Milestone Event is achieved. If Otsuka or its Affiliates or Sublicensees achieve all of the Sales Milestone Events, then the Sales Milestone Payments payable by Otsuka under this Section 9.2.2 (Sales Milestones) will not exceed $[***].

9.3 Royalties.

9.3.1 **Royalty Payments During the Initial Royalty Term**. Subject to the provisions of Section 9.3.2 (Royalty Reductions), Otsuka will pay to Ionis royalties based on the Net Sales of a Licensed Product by Otsuka and its Affiliates and Sublicensees in the Otsuka Territory at the rates set forth in Table 9.3.1 below (the "***Initial Royalties***"), on a Licensed Product-by-Licensed Product and country-by-country basis, commencing on the first sale of such Licensed Product that results in Net Sales of such Licensed Product in such country and ending on the latest to occur of (a) the [***] anniversary of the First Commercial Sale of such Licensed Product in such country, (b) the expiration of the last Valid Claim in the [***] that Cover such Licensed Product in such country [***], and (c) loss of Regulatory Exclusivity of such Licensed Product in such country (the "***Initial Royalty Term***").

Table 9.3.1– Royalty Rates for the Licensed Products	
Calendar Year Net Sales of all Licensed Products in the Otsuka Territory	***Royalty Rate***
Portion of annual Net Sales of all Licensed Products in the Otsuka Territory that is [***]	[***]%
Portion of annual Net Sales of all Licensed Products in the Otsuka Territory that are [***]	[***]%
Portion of annual Net Sales of all Licensed Products in the Otsuka Territory that are [***]	[***]%

By way of example only, if Otsuka receives [***] in Net Sales of all Licensed Products during a given Calendar Year in the Otsuka Territory, then Otsuka would owe Ionis a royalty of [***] (as converted into U.S. Dollars in accordance with Section 9.8 (Method of Payment; Exchange Rate)).

9.3.2 **Royalty Reductions**.

(a) **Generic Approval**. On a country-by-country and Licensed Product-by-Licensed Product basis, if at any time during the Initial Royalty Term a Generic Product receives Regulatory Approval in a country in the Otsuka Territory, then, subject to Section 9.3.2(e) (Royalty Reductions Floor), the royalty rates set forth in Table 9.3.1 will be reduced by [***] for such Licensed Product in such country.

(b) **Third Party Payments**. Subject to Section 9.3.2(e) (Royalty Reductions Floor), Otsuka may credit [***] of [***] in a country in the Otsuka Territory in a Calendar Quarter during the Royalty Term against the Royalties due and payable by Otsuka to Ionis on the Net Sales for such Licensed Product in such country in such Calendar Quarter; *provided* that the terms of this Section 9.3.2(b) (Third Party Payments) will not apply to any license agreement entered into without Ionis' prior written consent in violation of the terms of Section 10.5.3 (Settlement). For clarity, Otsuka will not have the right to offset any Third Party Payments arising out of, or allocable to, the Manufacture of a Licensed Product.

(c) [***]. Subject to Section 9.3.2(e) (Royalty Reductions Floor), on a Licensed Product-by-Licensed Product and country-by-country basis, if during any Calendar Quarter during the Initial Royalty Term for such Licensed Product in such country, (i) [***], and (ii) [***], then, commencing [***]; *provided* that, if [***], then [***].

(d) [***]. Subject to Section 9.3.2(e) (Royalty Reductions Floor), on a Licensed Product-by-Licensed Product and country-by-country basis, during the Initial Royalty Term for such Licensed Product in such country, if, [***].

(e) **Royalty Reductions Floor**. In no event will the Royalties due to Ionis for a Licensed Product in a country in the Otsuka Territory [***] set forth in this Section 9.3.2 (Royalty Reductions). Notwithstanding the foregoing, [***].

9.3.3 **Reduced Royalty Term**. On a Licensed Product-by-Licensed Product and country-by-country basis in the Otsuka Territory, following expiration of the Initial Royalty Term for a Licensed Product in a given country in the Otsuka Territory, Otsuka will pay Ionis a [***] royalty on the Net Sales of such Licensed Product by Otsuka and its Affiliates and Sublicensees in such country (the "***Reduced Royalties***" and together with the Initial Royalties, the "***Royalties***") until the later of (a) [***], and (b) [***] (the "***Reduced Royalty Term***" and together with the Initial Royalty Term, the "***Royalty Term***"). For clarity, on a Licensed Product-by-Licensed Product and country-by-country basis, [***].

9.3.4 **Royalty Payments and Reports**.

(a) [***]. Commencing with the Calendar Quarter during which the first sale of a Licensed Product is made that results in Net Sales anywhere in the Otsuka Territory, [***].

(b) **Royalty Report**. Commencing with the Calendar Quarter during which the first sale of a Licensed Product is made that results in Net Sales anywhere in the Otsuka Territory, within [***] after the end of each Calendar Quarter, Otsuka will provide to Ionis a written report (each, a "***Royalty Report***") setting forth in reasonable detail: (i) the gross sales of the Licensed Products sold by Otsuka or its Affiliate or Sublicensee in the Otsuka Territory in such Calendar Quarter; (ii) the aggregate Net Sales of the Licensed Products sold by Otsuka or its Affiliates or Sublicensees in the Otsuka Territory in such Calendar Quarter; (iii) all deductions and reductions used to determine the Net Sales of the Licensed Products for such Calendar Quarter or the Royalties payable with respect to the Licensed Products for such Calendar Quarter, including any reduction pursuant to Section 9.3.2 (Royalty Reductions) (if applicable); (iv) the exchange rates used to calculate the Royalties payable in U.S. Dollars; (v) any withholding taxes required to be made from such Royalties; and (vi) the quantity and description of the Licensed Products sold by Otsuka or its Affiliate or Sublicensee in the Otsuka Territory during such Calendar Quarter comprising such Net Sales. The Parties will seek to resolve any questions or issues related to a Royalty Report within [***] following receipt by Ionis of each Royalty Report.

(c) **Royalty Payments**. The information contained in each Royalty Report will be considered the Confidential Information of Otsuka. Following receipt of each Royalty Report, Ionis will [***] and, [***], Otsuka will pay the Royalties due hereunder for the Calendar Quarter covered by the applicable Royalty Report.

9.4 Other Amounts Payable. With respect to any amounts owed under this Agreement by one Party to the other for which no other invoicing and payment procedure is specified hereunder, within [***] after the end of each Calendar Quarter, each Party will provide an invoice, together with reasonable supporting documentation, to the other Party for such amounts owed in respect of such Calendar Quarter. The owing Party will pay any undisputed invoiced amounts within [***] after the date of the invoice, and any disputed amounts owed by a Party will be paid within [***] following resolution of the dispute.

9.5 **Financial Records and Audits**. Each Party will, and will require its Sublicensees and Subcontractors to, maintain complete and accurate records in accordance with such Party's Accounting Standards in sufficient detail to permit the other Party to confirm the accuracy of any amounts payable under this Agreement for at least the preceding [***], including (as applicable) any Eligible Cross-Territory Development Costs, Milestone Payments, Royalties, and sales of the Licensed Products (including all calculations of Net Sales). Upon reasonable prior notice, each Party agrees to permit such records to be open during regular business hours for examination by an independent certified public accountant selected by the auditing Party and reasonably acceptable to the audited Party for the sole purpose of verifying the accuracy of the financial reports furnished by the audited Party pursuant to this Agreement or of any payments made, or required to be made, by the audited Party pursuant to this Agreement; *provided* that such independent accounting firm is subject to written obligations of confidentiality and non-use applicable to each Party's Confidential Information that are at least as stringent as those set forth in Article 12 (Confidentiality). Such audit will not be (a) performed more frequently than [***], or (b) repeated for any Calendar Year or with respect to the same set of records (in each case, except for cause). Such auditor will not disclose the audited Party's Confidential Information to the auditing Party or to any Third Party, except to the extent such disclosure is necessary to verify the accuracy of the financial reports furnished by the audited Party or the amount of payments by the audited Party under this Agreement. The audited Party will pay any amounts shown to be owed to the auditing Party but unpaid within [***] after the accountant's report, *plus* interest (as set forth in Section 9.11 (Late Payments; Disputed Payments)) from the original due date solely if the audited Party is responsible for the discrepancy. If such examination of records reveals any overpayment by Ionis, then Otsuka will reimburse Ionis for the amount overpaid within [***] after the accountant's report, *plus* interest (as set forth in Section 9.11 (Late Payments; Disputed Payments)) from the original due date [***]. If such examination of records reveals any overpayment by Otsuka, then [***]. The auditing Party will bear the full cost of such audit unless such audit reveals an underpayment by the audited Party of more than [***] of the amount actually due for the time period being audited, in which case the audited Party will reimburse the auditing Party for the reasonable audit fees for such examination.

9.6 **No Refunds**. Except as expressly provided herein, all payments under this Agreement will be irrevocable, non-refundable, and non-creditable.

9.7 **Accounting Standards**. If a Party changes its general accounting principles from its then-current Accounting Standard (*e.g.*, from GAAP to IFRS) at any time during the Term, then at least [***] prior to adopting such change in principles, such Party will provide written notice to the other Party of such change. A Party may not change its general accounting principles to any accounting standard other than GAAP or IFRS without the prior written approval of the other Party.

9.8 **Method of Payment; Exchange Rate**. All amounts to be paid pursuant to this Agreement will be made in U.S. Dollars and will be paid by wire transfer in immediately available funds to a bank account designated by the receiving Party. The rate of exchange to be used in computing the amount of currency equivalent in U.S. Dollars owed to a Party under this Agreement will be the Selling Party's then-current standard exchange rate methodology employed for the translation of foreign currency sales into U.S. Dollars in accordance with its Accounting Standards and consistently applied during the period.

9.9 **Blocked Payments**. If by reason of Applicable Law in any country or jurisdiction, it becomes impossible or illegal for a Party to transfer, or have transferred on its behalf, payments owed the other Party hereunder, then such Party will promptly notify the other Party of the conditions preventing such transfer and use reasonable efforts to deposit such payments in U.S. Dollars. If, after using reasonable efforts, such Party is not able to deposit such payments in U.S. Dollars, then such payments will be deposited in local currency in the relevant country to the credit of the other Party in a recognized banking institution designated by the other Party or, if none is designated by the other Party within [***], in a recognized banking institution selected by the transferring Party, as the case may be, and identified in a written notice given to the other Party.

9.10 Taxes.

9.10.1 **Taxes on Income**. Each Party will be solely responsible for the payment of any and all income Taxes levied on account of all payments it receives under this Agreement.

9.10.2 **Withholding Tax**. Any and all payments made pursuant to this Agreement will be paid without deduction or withholding for any Taxes, except as required by Applicable Law. To the extent a Party is required by Applicable Law to deduct or withhold Taxes on any payment to the other Party (the "***Withheld Amount***"), such Party will remit such Withheld Amount to the proper Governmental Authority in a timely manner and promptly transmit to the other Party an official Tax certificate or other evidence of any withholding sufficient to enable the other Party to claim available credits for such Withheld Amount. The withholding Party will have the right to deduct such Withheld Amount from payment due to the other Party. For the avoidance of doubt, to the extent such Withheld Amount is so withheld and remitted in accordance with this Section 9.10.2 (Withholding Tax), such Withheld Amount will be treated for all purposes of this Agreement as having been paid to the other Party.

9.10.3 **Tax Cooperation**. The Parties agree to cooperate with one another in accordance with Applicable Law and use reasonable efforts to [***] in respect of payments made by each Party to the other Party under this Agreement. Without limiting the generality of the foregoing, each Party will provide the other with any Tax forms and other information that may be reasonably necessary to [***] based on an applicable treaty or otherwise, including a properly completed Internal Revenue Service ("***IRS***") Form W-9 or appropriate IRS Form W-8, as applicable, before a payment is made. If any Tax form or other information a Party previously delivered expires or becomes obsolete or inaccurate in any respect, then such Party will provide the other Party with an updated version of such form or certification or promptly notify the other Party in writing of its legal inability to do so. Each Party will provide the other Party with reasonable assistance to enable the recovery, as permitted by Applicable Law, of withholding Taxes or similar obligations resulting from payments made under this Agreement, such recovery to be for the benefit of the Party bearing such withholding Tax.

9.10.4 **Changes in Domicile**. Notwithstanding any provision to the contrary in this Agreement, including Section 9.10.2 (Withholding Tax), if as a result of a Party assigning, transferring, or conveying rights under this Agreement to an Affiliate or changing its domicile, additional Taxes become due that would not otherwise have been due hereunder with respect to payments under this Agreement, then such Party will be responsible for all such additional withholding Taxes.

9.11 Late Payments; Disputed Payments. Any undisputed payments or portions thereof due hereunder that are not paid on or before the date such payments are due under this Agreement will bear interest from the due date until the date of payment at a per-annum rate equal to the lesser of: (a) [***] percentage points above the prime rate as published by *The Wall Street Journal* or any successor thereto; or (b) the maximum rate permitted by Applicable Law. If a Party disputes an invoice or other payment obligation under this Agreement, then such Party will timely pay the undisputed amount of the invoice or other payment obligation, and the Parties will resolve such dispute in accordance with Article 15 (Dispute Resolution; Governing Law).

ARTICLE 10
INTELLECTUAL PROPERTY

10.1 Inventions.

10.1.1 **Ownership of Background Intellectual Property**. As between the Parties, and subject to the licenses granted under this Agreement, each Party retains all rights, title, and interests in and to all Patent Rights and Know-How that such Party owns or Controls as of the Effective Date or that it develops or otherwise acquires after the Effective Date outside the performance of the activities under this Agreement.

10.1.2 **Ownership of Arising Intellectual Property**. As between the Parties, ownership of all Collaboration Know-How will be as follows:

(a) Ionis will be the sole owner of any (i) Collaboration Know-How that is developed or invented solely by Representatives of Ionis or its Affiliates or its or their licensees (other than Otsuka), Sublicensees, or Subcontractors, or any Persons contractually required to assign or license such Collaboration Know-How to Ionis or any Affiliate of Ionis ("***Ionis Collaboration Know-How***"), and (ii) Patent Rights that Cover the Ionis Collaboration Know-How ("***Ionis Collaboration Patent Rights***"), and will retain all of its rights thereto, subject to any rights or licenses expressly granted by Ionis to Otsuka under this Agreement.

(b) Otsuka will be the sole owner of any (i) Collaboration Know-How that is developed or invented solely by Representatives of Otsuka or its Affiliates or its or their licensees (other than Ionis), Sublicensees, or Subcontractors, or any Persons contractually required to assign or license such Collaboration Know-How to Otsuka or any Affiliate of Otsuka ("***Otsuka Collaboration Know-How***"), and (ii) Patent Rights that Cover the Otsuka Collaboration Know-How ("***Otsuka Collaboration Patent Rights***"), and will retain all of its rights thereto, subject to any rights or licenses expressly granted by Otsuka to Ionis under this Agreement.

(c) Each Party will own an equal, undivided share of all Joint Collaboration Technology.

10.1.3 **Disclosure; Inventorship**.

(a) **Invention Disclosure**. Each Party will promptly disclose to the other Party all Inventions within the Collaboration Know-How developed or invented during the Term by or on behalf of such Party, in each case, as soon as practicable prior to an intended public disclosure of such Invention and prior to the filing of a patent application thereon. Each Party will also promptly respond to reasonable requests from the other Party for additional information relating thereto.

(b) **Inventions by a Party**. Inventorship for Inventions and discoveries (including Know-How) first invented or developed during the course of the performance of activities under this Agreement will be determined in accordance with United States Patent Laws for determining inventorship.

(c) **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 10 (Intellectual Property) 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 respect to any submissions, filings or other activities in support thereof. The Parties acknowledge and agree that this Agreement is a "*joint research agreement*" as defined in 35 U.S.C. § 100(h).

10.1.4 **Practice Under and Other Use of Joint Collaboration Technology**. Subject to the rights granted under and the restrictions set forth in this Agreement (including the licenses granted under Article 2 (Licenses)), each Party will be entitled to the free use and enjoyment of all Joint Collaboration Technology and neither Party will have any obligation to account to the other Party for profits, or to obtain any approval of the other Party to license, assign, or otherwise exploit any Joint Collaboration Technology by reason of joint ownership thereof. Each Party hereby waives any right it may have under the Applicable Law of any jurisdiction to require any such approval or accounting. To the extent any further consent is required to enable a Party to so license or exploit its interest in the Joint Collaboration Technology, the other Party will grant consent promptly upon request. Without limitation, each Party will cooperate with the other Party if the Parties determine to apply for U.S. or foreign patent protection for any Joint Collaboration Technology and will obtain the cooperation of the individual inventors of any such Joint Collaboration Technology**.**

10.1.5 **Representative Assignment**. Each Party and its Affiliates will, and will cause its licensees, Sublicensees and Subcontractors to, enter into an agreement or employment policy with each of its Representatives performing activities related to Development, Manufacture, or Commercialization of a Licensed Product that (a) compels prompt disclosure to such Party (or its Affiliate, licensee, Sublicensee or Subcontractor, as applicable) of all Collaboration Know-How and Collaboration Patent Rights discovered, developed, invented, or filed by such Representative during any performance of such Development, Manufacture or Commercialization activities; and (b) automatically assigns to such Party (or its Affiliate, licensee, Sublicensee or Subcontractor, as applicable) all rights, title, and interests in and to all Collaboration Know-How and Collaboration Patent Rights, and requires each Representative to execute all documents and take such other actions as may be necessary to effectuate such assignment (or, if such assignment is not feasible, provides for such Party's (or its Affiliate's, licensee's, Sublicensee's or Subcontractor's, as applicable) joint ownership of, or an irrevocable, royalty-free license to such Party (or its Affiliate, licensee, Sublicensee or Subcontractor, as applicable) under, all Collaboration Know-How and Collaboration Patent Rights, with the right to sublicense to the other Party as contemplated in this Agreement), *provided* that the foregoing will not apply with respect to improvements to background technology of a Subcontractor.

10.2 Patent Prosecution.

10.2.1 **Ionis Patent Rights and Joint Collaboration Patent Rights**.

(a) **Right to Prosecute**. As between the Parties, Ionis will have the (i) first right, in its sole discretion, to control the Patent Prosecution of all Ionis Product-Specific Patents in the Otsuka Territory and all Joint Collaboration Patent Rights worldwide, and (ii) sole right, in its sole discretion, to control the Patent Prosecution of all (A) Ionis Product-Specific Patents in the Ionis Territory, and (B) Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents, in each case, worldwide (collectively, ((i) and (ii)), the "***Ionis Prosecuted Patent Rights***"). Upon Ionis' request, Otsuka will obtain any necessary assignment documents for Ionis with respect to the Patent Prosecution of Ionis Prosecuted Patent Rights, will render all signatures that will be necessary for such patent filings, and will assist Ionis in all other reasonable ways that are necessary for the issuance of Ionis Prosecuted Patent Rights as well as for the Patent Prosecution of Ionis Prosecuted Patent Rights, and Ionis will reimburse Otsuka's reasonable External Costs incurred in connection therewith. Ionis will be responsible for [***] of the costs and expenses incurred with respect to the Patent Prosecution of all Ionis Product-Specific Patents, Ionis Core Technology Patents and Ionis Manufacturing and Analytical Patents throughout the world and for [***] of the costs and expenses incurred with respect to the Patent Prosecution of Joint Collaboration Patent Rights in the Ionis Territory. Otsuka will be responsible for [***] of the reasonable out-of-pocket costs incurred by or on behalf of Ionis with respect to the Patent Prosecution of the Joint Collaboration Patent Rights in the Otsuka Territory (including any maintenance fees owed to local patent offices for the Joint Collaboration Patent Rights in the Otsuka Territory), and Otsuka will reimburse Ionis for such costs within [***] after receiving an invoice with reasonable supporting documentation for such costs.

(b) **Review and Consult**. Ionis will consult with Otsuka and keep Otsuka reasonably informed regarding the Patent Prosecution of the Ionis Product-Specific Patents in the Otsuka Territory and the Patent Prosecution of the Joint Collaboration Patent Rights worldwide and will provide Otsuka with all substantive correspondence received from any patent authority in connection therewith no later than [***] after receipt thereof. In addition, Ionis will provide Otsuka with drafts of proposed substantive filings in the Otsuka Territory and correspondence to any patent authority in the Otsuka Territory in connection with the Patent Prosecution of the Ionis Product-Specific Patents and with drafts of proposed substantive filings in the Territory and correspondence to any patent authority in the Territory in connection with the Patent Prosecution of Joint Collaboration Patent Rights, in each case for Otsuka's review and comment at least [***] prior to the submission of such proposed filings and correspondence, which comments (if any) Otsuka must provide no later than [***] after receipt of the applicable filing or correspondence. Ionis will consider in good faith Otsuka's reasonable comments on the Patent Prosecution of the Ionis Product-Specific Patents in the Otsuka Territory and the Joint Collaboration Patent Rights in the Territory, but Ionis will have final decision-making authority regarding Patent Prosecution of such Patent Rights under this Section 10.2.1(b) (Review and Consult).

(c) **Abandonment**. If, at any time during the Term, Ionis decides to cease the Patent Prosecution of a particular Ionis Product-Specific Patent in the Otsuka Territory, or a particular Joint Collaboration Patent Right in the Territory, then Ionis will provide written notice to Otsuka of such decision at least [***] prior to the date that such applicable Patent Right will become abandoned. Unless such written notice includes a reasonable strategic reason for ceasing such Patent Prosecution (e.g., continuing such Patent Prosecution would adversely affect Ionis' Patent Prosecution or litigation strategy), Otsuka may, upon written notice to Ionis, assume the Patent Prosecution of any such Patent Right at Otsuka's sole cost and expense. Without limiting the foregoing, with respect to any such Joint Collaboration Patent Right abandoned by Ionis, Ionis shall assign, and hereby does assign, to Otsuka all of its rights, title and interests in and to such Joint Collaboration Patent Right, and upon such assignment, such Joint Collaboration Patent Right shall be deemed an Otsuka Patent Right for all purposes of this Agreement.

10.2.2 **Otsuka Patent Rights**.

(a) **Right to Prosecute**. As between the Parties, Otsuka will have the first right to control the Patent Prosecution of all Otsuka Patent Rights throughout the world. Otsuka will be responsible for [***] of the costs and expenses incurred with respect to the Patent Prosecution of such Patent Rights throughout the world.

(b) **Review and Consult**. Otsuka will consult with Ionis and keep Ionis reasonably informed regarding the Patent Prosecution of the Otsuka Patent Rights and will provide Ionis with all substantive correspondence received from any patent authority in connection therewith no later than [***] after receipt thereof. In addition, Otsuka will provide Ionis with drafts of all proposed substantive filings and correspondence to any patent authority in connection with the Patent Prosecution of the Otsuka Patent Rights for Ionis' review and comment at least [***] prior to the submission of such proposed filings and correspondence, which comments (if any) Ionis must provide no later than [***] after receipt of the applicable filing or correspondence. Otsuka will consider in good faith Ionis' reasonable comments on the Patent Prosecution of the Otsuka Patent Rights, but will have final decision-making authority regarding Patent Prosecution of such Patent Rights under this Section 10.2.1(b) (Review and Consult).

(c) **Abandonment**. If, at any time during the Term, Otsuka ceases the Patent Prosecution of a particular Otsuka Patent Right, then Otsuka will provide written notice to Ionis of such decision at least [***] prior to the date on which such Patent Right will become abandoned. Unless such written notice includes a reasonable strategic reason for ceasing such Patent Prosecution (e.g., continuing such Patent Prosecution would adversely affect Otsuka's Patent Prosecution or litigation strategy), Ionis may, upon written notice to Otsuka, assume the Patent Prosecution of any such Patent Right at Ionis' sole cost and expense.

10.3 Enforcement Against Third Party Infringement or Misappropriation.

10.3.1 **Notice of Infringement or Misappropriation**. Each Party will promptly notify the other of any apparent, threatened, or actual Competitive Infringement of which it becomes aware.

10.3.2 **Otsuka's Enforcement Right**. Otsuka will have the first right, but not the obligation, to enforce [***] against any Competitive Infringement in the Otsuka Territory and at its own cost and expense and using counsel of its own choice; *provided* that, (a) [***] Ionis will be entitled to attend any substantive meetings, hearings, or other proceedings related to such infringement or misappropriation suit (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such infringement or misappropriation suit prior to filing or submission of such documents, and (b) with respect [***] Otsuka shall keep Ionis reasonably informed of the status of any substantive meetings, hearings, or other proceedings related to such infringement or misappropriation suit. If Otsuka fails to initiate a suit or take other action to abate any such Competitive Infringement within the earlier of: (i) [***] and (ii) [***], then, in either case, Ionis will have the second right, but not the obligation, to attempt to resolve such Competitive Infringement, at its own expense, including the filing of an infringement or misappropriation suit, as applicable, to enforce the applicable Patent Rights or Know-How using counsel of its own choice; *provided* that, if Otsuka notifies Ionis during [***] that it is electing not to take steps to enforce the applicable Patent Rights against such Competitive Infringement [***].

10.3.3 **Ionis' Enforcement Right**. Ionis will have the sole right, but not the obligation, to enforce [***] against any Competitive Infringement in the Territory, in each case ((a) and (b)), at its own cost and expense and using counsel of its own choice; *provided* that Ionis shall keep Otsuka reasonably informed of the status of any substantive meetings, hearings, or other proceedings related to any infringement or misappropriation suit to enforce [***] against any Competitive Infringement in the Otsuka Territory. Ionis will have the first right, but not the obligation, to enforce any [***] in the Ionis Territory, in each case, at its own expense and using counsel of its own choice; *provided* that Otsuka will be entitled to attend any substantive meetings, hearings, or other proceedings related to such infringement or misappropriation suit (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such infringement or misappropriation suit prior to filing or submission of such documents. If Ionis fails to initiate a suit or take other action to abate any such Competitive Infringement with respect to [***] in the Ionis Territory within the earlier of: (a) [***] and (b) [***], then, in either case, Otsuka will have the second right, but not the obligation, to attempt to resolve such Competitive Infringement, at its own expense, including the filing of an infringement or misappropriation suit, as applicable, to enforce the applicable Otsuka Technology or Joint Collaboration Technology using counsel of its own choice; *provided* that, if Ionis notifies Otsuka during [***] that it is electing not to take steps to enforce the applicable Patent Rights against such Competitive Infringement [***].

10.3.4 **Allocation of Recoveries**. Any recoveries resulting from an enforcement action relating to a claim of Competitive Infringement in the Territory will be first applied against payment of each Party's costs and expenses in connection therewith. Any such recoveries in excess of such costs and expenses will be [***]; *provided* that [***].

10.3.5 **Cooperation; Procedures**. At the request and expense of the Party bringing an infringement or misappropriation action under this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation), the other Party will provide reasonable assistance and cooperation in any such action (including entering into a common interest agreement if reasonably deemed necessary by any Party) and agrees to be joined as a party to the suit if necessary for the initiating Party to bring or continue an infringement or misappropriation action hereunder. In addition, the Party bringing an infringement or misappropriation action under this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation) will provide the other Party with copies of all pleadings and other documents in advance of filing with the court and will consider reasonable input from the other Party during the course of the action. For clarity, the Party bringing an infringement or misappropriation action under this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation) will control such infringement or misappropriation action subject to the terms of this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation). Neither Party may settle any action or proceeding brought under this Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation) or knowingly take any other action in the course thereof that disclaims, limits the scope of, admits the invalidity or unenforceability of, or grants a license, covenant not to sue or similar immunity under a Patent Right Controlled by the other Party without first obtaining the written consent of the Party that Controls the relevant Patent Right. Furthermore, Ionis may not [***]. The Parties will reasonably assist each other and cooperate with each other, at their own expense, in any such investigation, pre-litigation preparation, or litigation to ensure that there is an aligned global litigation and enforcement strategy.

10.4 **Defense of Third-Party Patent Challenges**. Each Party will promptly notify the other Party in writing after becoming aware of an actual or threatened Patent Challenge by a Third Party of any Ionis Patent Right, Otsuka Patent Right, and Joint Collaboration Patent Right (each, a "***Third Party Patent Challenge***").

10.4.1 **Otsuka's Right to Defend**. Subject to the terms of Section 10.4.3 (Cooperation; Procedures), and except as may be otherwise agreed by the Parties, Otsuka will have the first right, but not the obligation, to control the defense of any Third Party Patent Challenge relating to an Otsuka Patent Right or Joint Collaboration Patent Right in the Otsuka Territory, and to compromise, litigate, settle, or otherwise dispose of any such challenge, in each case at its own expense using counsel of its own choice; *provided* that (a) with respect to a Joint Collaboration Patent Right, Ionis will be entitled to attend any substantive meetings, hearings, or other proceedings related to such Third Party Patent Challenge (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such Third Party Patent Challenge, and (b) with respect to an Otsuka Patent Right, Otsuka shall keep Ionis reasonably informed of the status of any substantive meetings, hearings, or other proceedings related to such Third Party Patent Challenge, and if Otsuka fails to initiate the defense of such Third Party Patent Challenge of a Patent Right in the Otsuka Territory within [***] after the notice provided under Section 10.4 (Defense of Third Party Patent Challenges), or otherwise abandons or elects not to continue any such defense once initiated, then Ionis will have the second right, but not the obligation, to control the defense of such Third Party Patent Challenge at its own expense using counsel of its own choice.

10.4.2 **Ionis' Right to Defend**. Ionis will have the sole right, but not the obligation, to control the defense of any Third Party Patent Challenge relating to an (a) Ionis Product-Specific Patent in the Ionis Territory or (b) Ionis Core Technology Patent or Ionis Manufacturing and Analytical Patent in the Territory, and to compromise, litigate, settle, or otherwise dispose of any such challenge, in each case, at its own expense using counsel of its own choice. Subject to the terms of Section 10.4.3 (Cooperation; Procedures), Ionis will have the first right, but not the obligation, to control the defense of any Third Party Patent Challenge relating to an (i) Otsuka Patent Right or Joint Collaboration Patent Right in the Ionis Territory or (ii) Ionis Product-Specific Patent in the Otsuka Territory and to compromise, litigate, settle, or otherwise dispose of any such challenge, at its own expense using counsel of its own choice; *provided* that Otsuka will be entitled to attend any substantive meetings, hearings, or other proceedings related to such Third Party Patent Challenge (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such Third Party Patent Challenge. If Ionis fails to initiate the defense of such Third Party Patent Challenge of an Otsuka Patent Right or Joint Collaboration Patent Right in the Ionis Territory or an Ionis Product-Specific Patent in the Otsuka Territory, in each case, within [***] after the notice provided under Section 10.4 (Defense of Third Party Patent Challenges), or otherwise abandons or elects not to continue any such defense once initiated, then Otsuka will have the second right, but not the obligation, to control the defense of such Third Party Patent Challenge at its own expense using counsel of its own choice.

10.4.3 **Cooperation; Procedures**. At the request and expense of the Party controlling the defense of any Third Party Patent Challenge under this Section 10.4 (Defense of Third Party Patent Challenges), the other Party will provide reasonable assistance and cooperation in any such action. In addition, the Party controlling the defense of any Third Party Patent Challenge under this Section 10.4 (Defense of Third Party Patent Challenges) will provide the other Party with copies of all pleadings and other documents to be filed with the court and will consider reasonable input from the other Party during the course of the action. Otsuka may not settle any action or proceeding brought or defended under this Section 10.4 (Defense of Third-Party Patent Challenges) or knowingly take any other action in the course thereof without Ionis' prior written consent, unless such action or proceeding solely concerns the Otsuka Patent Rights. Ionis may not settle any action or proceeding brought or defended under this Section 10.4 (Defense of Third-Party Patent Challenges) or knowingly take any other action in the course thereof with respect to the Ionis Product-Specific Patents or Joint Collaboration Patent Rights in the Otsuka Territory, without Otsuka's prior written consent not to be unreasonably withheld, conditioned or delayed. The Parties will reasonably assist each other and cooperate with each other, at their own expense, in any such investigation, pre-litigation preparation, or litigation to ensure that there is an aligned global litigation strategy. Notwithstanding the above, in the case of any invalidity or unenforceability claims arising in an enforcement action under Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation), the Party controlling the enforcement action pursuant to Section 10.3 (Enforcement Against Third Party Infringement or Misappropriation) shall control the response to such invalidity or unenforceability claims, *provided* such Party may not admit invalidity or unenforceability of any Patent Right Controlled by the other Party without the prior written consent of the other Party.

10.5 Third Party Infringement Claims.

10.5.1 **Infringement Claim; Patent Challenges of Third-Party IP**. If a Third Party asserts that a Patent Right controlled by it is, or will be, infringed by the Exploitation of a Licensed Product in the Territory in accordance with this Agreement, then the Party first obtaining knowledge of such claim will promptly provide the other Party with prompt written notice thereof and the related facts in reasonable detail.

10.5.2 **Responsibility to Defend**. During the Term of this Agreement, if a Third Party asserts that a Patent Right controlled by such Third Party is infringed, or will be infringed, by the Exploitation of a Licensed Product, then the Parties will promptly discuss the matter and the appropriate course of action. If the Parties cannot agree on a course of action within [***] following the date on which the Parties receive notice of such Third Party claim, then, subject to Article 13 (Indemnification): (a) Ionis will have the sole right, but not the obligation, to defend such claim in the Ionis Territory using counsel of its own choosing, and (b) Otsuka will have the first right, but not the obligation, to defend such claim in the Otsuka Territory using counsel of its own choosing. If Otsuka does not take affirmative steps to defend such claim in the Otsuka Territory within [***] (or such shorter period of time as is legally required to answer to such claim) and does not inform Ionis within such [***] period that it is electing not to defend such claim for strategic reasons intended to maintain the commercial value of the relevant Patent Rights or any product or subject matter Covered thereby or relating thereto, then Ionis may defend such claim in the Otsuka Territory. The Party defending such claim in the Otsuka Territory will (i) keep the other Party reasonably informed regarding any such assertion, including by providing the other Party with copies of all pleadings and other documents filed in any proceeding relating to such claim, (ii) consider reasonable input from the other Party during the course of the claim, and (iii) provide the other Party with the opportunity to attend any substantive meetings, hearings, or other proceedings related to such claim (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such claim prior to filing or submission of such documents. The Parties will reasonably assist each other and cooperate and share information with respect to any such claim. Each Party will bear its own costs and expenses with respect to any such claim.

10.5.3 **Settlement**. Subject to Article 13 (Indemnification), neither Party will pursue or enter into any settlement or license agreement with any Third Party with respect to the Patent Rights that are the subject of a claim brought by a Third Party that a Patent Right controlled by such Third Party is infringed by the Exploitation of a Licensed Product in the Otsuka Territory without the other Party's prior written consent, not to be unreasonably withheld, conditioned, or delayed. Subject to Article 13 (Indemnification), Otsuka will bear the costs of any amounts paid in settlement or to satisfy a judgment of a claim that the Exploitation of a Licensed Product infringes any Third Party Patent Right in the Otsuka Territory, except to the extent such costs [***].

10.6 Patent Challenges of Third-Party Patent Rights.

10.6.1 **Notice of Third-Party Patent Right**. If either Party becomes aware of a Third Party Patent Right that might form the basis for a claim that the Exploitation of a Licensed Product anywhere in the world infringes, or will infringe, such Patent Right, then the Party first obtaining knowledge of such Patent Right will promptly provide the other Party with written notice thereof and the related facts in reasonable detail, and the Parties will promptly meet to discuss the matter.

10.6.2 **Patent Challenges of Third-Party Patents**. Ionis will have the sole right, but not the obligation, to initiate a Patent Challenge of any such Third Party Patent Right in the Ionis Territory using counsel of its own choosing. Otsuka will have the first right, but not the obligation, to initiate a Patent Challenge of such Third Party Patent Right in the Otsuka Territory, and if Otsuka notifies Ionis that it does not intend to initiate such a Patent Challenge, Ionis will have the second right, but not the obligation, to do so; *provided* that, [***]. The Party initiating such Patent Challenge will (a) keep the other Party reasonably informed regarding any such Patent Challenge, including by providing the other Party with copies of all pleadings and other documents filed in any proceeding relating to such Patent Challenge, (b) consider reasonable input from the other Party during the course of the Patent Challenge, and (c) provide the other Party with the opportunity to attend any substantive meetings, hearings, or other proceedings related to such Patent Challenge (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such Patent Challenge prior to filing or submission of such documents. The Parties will reasonably assist each other and cooperate and share information with respect to any such Patent Challenge. Each Party will bear its own costs and expenses with respect to any such Patent Challenge; *provided, however,* that the Parties will each bear [***] of the reasonable out-of-pocket costs incurred with respect to any such Patent Challenge in the Otsuka Territory, and the non-controlling Party will reimburse the Party initiating such Patent Challenge in the Otsuka Territory for such costs within [***] after receiving an invoice with reasonable supporting documentation for such costs.

10.6.3 **Restrictions on Settlement**. Neither Party nor its Affiliates will pursue or enter into any settlement or license agreement with any Third Party with respect to the Patent Rights that are the subject of such Patent Challenge in the Otsuka Territory without the other Party's prior written consent.

10.7 Patent Term Extensions. With respect to any system for extending the term of Patent Rights in the Otsuka Territory established by any applicable Regulatory Authority during the Term that is similar to the patent term extension system in the U.S., [***] for making all decisions regarding patent term extensions of the Ionis Patent Rights or Joint Collaboration Patent Rights in the Otsuka Territory, including supplementary protection certificates and any other extensions that are now or become available in the future, that are applicable to the Ionis Patent Rights or Joint Collaboration Patent Rights licensed hereunder and that become available directly as a result of the Regulatory Approval of a Licensed Product in the Otsuka Territory; *provided* that Otsuka will consult with Ionis with respect to such decisions and consider in good faith the reasonable comments and concerns of Ionis.

10.8 Unified Patent Court. Otsuka will be solely responsible for making all decisions regarding the opting-out or opting-in of existing Patent Rights into the jurisdiction of the Unified Patent Court or the registration of Patent Rights with Unitary Effect; *provided* that Otsuka will consult with Ionis with respect to such decisions and will consider the comments and concerns of Ionis in good faith.

10.9 Common Interest. The Parties stipulate and agree that, with regard to such prosecution, maintenance, enforcement, and defense the interests of the Parties as collaborators and licensor and licensee are to obtain the strongest patent protection possible, and as such, are aligned and are legal in nature. The Parties stipulate and agree that they have not waived, and nothing in this Agreement constitutes a waiver of, any legal privilege concerning the Patent Rights under this Article 10 (Intellectual Property), including privilege under the common interest doctrine and similar or related doctrines. Notwithstanding any provision to the contrary set forth in this Agreement, to the extent a Party has a good faith belief that any information required to be disclosed by such Party to the other Party under this Article 10 (Intellectual Property) is protected by attorney-client privilege or any other applicable legal privilege or immunity, such Party will not be required to disclose such information and the Parties will in good faith cooperate to agree upon a procedure (including entering into a specific common interest agreement, disclosing such information on a "for counsel eyes only" basis or similar procedure) under which such information may be disclosed without waiving or breaching such privilege or immunity.

10.10 Product Trademarks.

10.10.1 **Ownershi**p.

(a) **Unitary Product Trademark**. Ionis shall, at its sole cost and expense, develop, and shall use Commercially Reasonable Efforts to obtain and maintain, a unitary Trademark (and back-up Trademarks thereof) to be used for the Licensed Products worldwide (the "***Unitary Product Trademark***"); *provided however*, [***]. Ionis will own all right, title, and interest in and to the Unitary Product Trademark. Otsuka will use the Unitary Product Trademark in the Otsuka Territory to the extent required by and in accordance with the Otsuka Territory Brand Strategic and Operating Plan, subject to Section 6.4 (Global Brand Strategic and Operating Plan) and Section 6.5 (Otsuka Territory Brand Strategic and Operating Plan).

(b) **Ownership of Otsuka Product Trademarks**. As between the Parties, Otsuka will have the sole right to determine and will own all right, title, and interest in and to any Trademarks, other than the Unitary Product Trademark, to be created or used by Otsuka or its Affiliates or its or their Sublicensees for the Exploitation of Licensed Product in the Otsuka Territory excluding any trademarks, service marks, names, or logos that include any corporate name or logo of the Parties or their Affiliates or its or their Sublicensees ("***Otsuka Product Trademarks***"); *provided* that such Otsuka Product Trademarks are consistent with the Global Brand Strategic and Operating Plan. Ionis will not [***]. Ionis will not [***].

(c) **Ownership of Ionis Product Trademarks**. As between the Parties, Ionis will have the sole right to determine and will own all right, title, and interest in and to the Trademarks (other than the Unitary Product Trademark) to be used by Ionis or its Affiliates or its or their Sublicensees or licensees for the Exploitation of Licensed Product in the Ionis Territory excluding any trademarks, service marks, names, or logos that include any corporate name or logo of the Parties or their Affiliates or its or their Sublicensees or licensees ("***Ionis Product Trademarks***"); *provided* that such Ionis Product Trademarks are consistent with the Global Brand Strategic and Operating Plan. Otsuka will not [***]. Otsuka will not [***].

10.10.2 **Notice**. Each Party will provide to the other Party prompt written notice of any actual or threatened infringement of the Otsuka Product Trademarks or Ionis Product Trademarks in the Territory and of any actual or threatened claim that the use of the Otsuka Product Trademarks or Ionis Product Trademarks in the Territory violates the rights of any Third Party, in each case, of which such Party becomes aware.

10.10.3 **Prosecution of Product Trademarks**.

(a) **Unitary Product Trademark**. Ionis shall be responsible, at its sole discretion and cost and expense using counsel of its own choice, for the filing, prosecution, registration and maintenance (including the defense of opposition proceedings and any equivalent proceedings and including any legal actions to prevent or exclude Third Party Trademark registrations that are confusingly similar to the Unitary Product Trademark) of the Unitary Product Trademark in the Territory throughout the Term. Ionis shall keep Otsuka informed of material progress with regard to the prosecution, registration, and maintenance of the Unitary Product Trademark in the Otsuka Territory, including the content and timing of the filing of the Unitary Product Trademark in the Otsuka Territory, [***], and Ionis shall [***] the Unitary Product Trademark in the Otsuka Territory**.**

(b) **Otsuka Product Trademarks**. Otsuka will have the sole right to register, prosecute and maintain the Otsuka Product Trademarks in the Territory using counsel of its own choice. All costs and expenses of registering, prosecuting and maintaining the Otsuka Product Trademarks in the Territory will be borne solely by Otsuka.

(c) **Ionis Product Trademarks**. Ionis will have the sole right to register, prosecute and maintain the Ionis Product Trademarks in the Territory using counsel of its own choice. All costs and expenses of registering, prosecuting and maintaining the Ionis Product Trademarks in the Territory will be borne solely by Ionis.

10.10.4 **Enforcement of Product Trademarks**.

(a) **Unitary Product Trademark**. During the Term, each Party will promptly notify the other Party in writing of any alleged, threatened or actual infringement, dilution, misappropriation or other violation of or unfair trade practices or any other like offense by a Third Party relating to the Unitary Product Trademark in the Otsuka Territory ("***Otsuka Territory Trademark Infringement***"). Otsuka will have the first right, but not the obligation, to take any reasonable measures it deems appropriate with respect to any Otsuka Territory Trademark Infringement, using counsel of its own choice, and at its own cost and expense, including initiating or prosecuting an infringement, misappropriation or other appropriate suit or action to enforce the Unitary Product Trademark in the Otsuka Territory and, if requested by Otsuka, Ionis shall (i) join as a party to such suit or action and execute and cause its Affiliates to execute all documents necessary for Otsuka to initiate and maintain such suit or action and (ii) provide reasonable assistance to Otsuka in connection with such suit or action. Notwithstanding the foregoing, if Otsuka does not inform Ionis that it intends to initiate a suit or take other action against an Otsuka Territory Trademark Infringement within [***] after Otsuka becoming aware of such Otsuka Territory Trademark Infringement and does not [***] within such [***], then Ionis will have the second right, but not the obligation, to initiate a suit or take other action against such Otsuka Territory Trademark Infringement at its own cost and expense. Any recoveries resulting from such suit or other action will be first applied against payment of each Party's costs and expenses in connection therewith. Any such recoveries in excess of such costs and expenses will be [***].

(b) **Otsuka Product Trademarks**. Otsuka will have the sole right to take such action as Otsuka deems necessary against a Third Party based on any alleged, threatened or actual infringement, dilution, misappropriation or other violation of or unfair trade practices or any other like offense relating to, the Otsuka Product Trademarks by a Third Party in the Territory, at its sole cost and expense and using counsel of its own choice. Otsuka will retain any damages or other amounts collected in connection therewith.

(c) **Ionis Product Trademarks**. Ionis will have the sole right to take such action as Ionis deems necessary against a Third Party based on any alleged, threatened or actual infringement, dilution, misappropriation or other violation of or unfair trade practices or any other like offense relating to, the Ionis Product Trademarks by a Third Party in the Territory, at its sole cost and expense and using counsel of its own choice. Ionis will retain any damages or other amounts collected in connection therewith.

10.10.5 **Third Party Claims**.

(a) **Unitary Product Trademark**. If a Third Party brings suit alleging that Otsuka's or its Affiliate's or Sublicensee's Exploitation of a Licensed Product in the Otsuka Territory infringes or will infringe such Third Party's Trademarks or that the use or registration of the Unitary Product Trademark in the Otsuka Territory infringes, dilutes, misappropriates or otherwise violates any Trademark or other right of such Third Party ("***Trademark Infringement Suit***"), then the Party against whom such suit is brought will promptly notify the other Party of such Trademark Infringement Suit and Otsuka will have the first right, but not the obligation, to defend such Trademark Infringement Suit using counsel of its own choice. If Otsuka does not take affirmative steps to defend such Trademark Infringement Suit within [***] (or such shorter period of time as is legally required to answer to such suit) and does not [***], then Ionis may defend such Trademark Infringement Suit. The Party defending such Trademark Infringement Suit will (i) keep the other Party reasonably informed regarding such suit, including by providing the other Party with copies of all pleadings and other documents filed in any proceeding relating to such suit, (ii) consider reasonable input from the other Party during the course of the suit, and (iii) provide the other Party with the opportunity to attend any substantive meetings, hearings, or other proceedings related to such suit (together with its own counsel, at its own expense) and to review and comment on all substantive documents related to such suit prior to filing or submission of such documents. The Parties will reasonably assist each other and cooperate and share information with respect to any such suit. The Parties will [***] all of the costs incurred by either Party in defending a Trademark Infringement Suit and any and all damages paid in settlement or to satisfy a judgment in a Trademark Infringement Suit. Neither Party will enter into any settlement of a Trademark Infringement Suit that is instituted or threatened to be instituted against the other Party without the other Party's prior written consent, not to be unreasonably withheld, conditioned or delayed; *provided* that such consent will not be required if such settlement includes a release of all liability in favor of, and does not impose any obligation on, the other Party and contains no admission of liability by such settling Party. Further, neither Party shall settle or compromise any Trademark Infringement Suit, or knowingly take any other action in the course thereof, in a manner that materially adversely affects the other Party's rights or interests, without the other Party's prior written consent.

(b) **Otsuka Product Trademarks**. Otsuka will have the sole right to defend against and settle any alleged, threatened or actual claim by a Third Party that the use or registration of the Otsuka Product Trademarks in the Territory infringes, dilutes, misappropriates or otherwise violates any Trademark or other right of that Third Party or constitutes unfair trade practices or any other like offense or any other claims as may be brought by a Third Party against a Party in connection with the use of the Otsuka Product Trademarks with respect to the Licensed Products in the Otsuka Territory, at its sole cost and expense and using counsel of its own choice. Otsuka will retain any damages or other amounts collected in connection therewith.

(c) **Ionis Product Trademarks**. Ionis will have the sole right to defend against and settle any alleged, threatened or actual claim by a Third Party that the use or registration of the Ionis Product Trademarks in the Territory infringes, dilutes, misappropriates or otherwise violates any Trademark or other right of that Third Party or constitutes unfair trade practices or any other like offense or any other claims as may be brought by a Third Party against a Party in connection with the use of the Ionis Product Trademarks with respect to the Licensed Products in the Ionis Territory, at its sole cost and expense and using counsel of its own choice. Ionis will retain any damages or other amounts collected in connection therewith.

10.10.6 **Housemarks**. The Parties, through the JSC, in consultation with regulatory experts, will [***].

10.10.7 **Cooperation**. Each Party will, and will cause its Affiliates to, promptly assist and cooperate with the other Party, as may be reasonably requested by a Party from time to time, in connection with its activities set forth in this Section 10.10 (Product Trademarks), including where necessary, furnishing a power of attorney solely for such purpose or joining in, or being named as a necessary party to, such action, and providing access to relevant documents and other evidence; *provided* that, except as provided otherwise in this Section 10.10 (Product Trademarks) with respect to [***], the requesting Party will reimburse the other Party for its [***] incurred in connection therewith.

ARTICLE 11
REPRESENTATIONS, WARRANTIES, AND COVENANTS

11.1 Mutual Representations and Warranties. Each of Otsuka and Ionis hereby represents and warrants to the other Party as of the Effective Date that:

11.1.1 It is a corporation or limited company duly organized, validly existing, and in good standing under the laws of the jurisdiction of its organization, and it has the full right, power, and authority to enter into this Agreement and to perform its obligations hereunder.

11.1.2 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.

11.1.3 The execution, delivery, and performance of this Agreement by it has been duly authorized by all requisite corporate action.

11.1.4 The execution and delivery of this Agreement and the performance of its obligations hereunder (a) do not conflict with or violate any requirement of Applicable Law or any provision of its articles of incorporation, bylaws, limited partnership agreement, or any similar instrument, as applicable, in any material way, and (b) do not conflict with, violate, or breach or constitute a default or require any consent under, any Applicable Law or any contractual obligation or court or administrative order by which it is bound.

11.1.5 It has not been debarred or suspended under 21 U.S.C. §335(a) or (b), is not the subject of a conviction described in Section 306 of the FD&C Act, has not been and is not excluded from a federal or governmental health care program, debarred from federal contracting, convicted of or pled *nolo contendere* to any felony, or to any federal or state legal violation (including misdemeanors) relating to prescription drug products or fraud, is not subject to OFAC sanctions or on the OFAC list of specially designated nationals, and is not subject to any similar sanction of any Governmental Authority in the Territory ("***Debarred/Excluded***"), and no proceeding that could result in it being Debarred/Excluded is pending, and neither it nor any of its Affiliates has used, in any capacity in the performance of obligations relating to the Licensed Products, any employee, subcontractor, consultant, agent, representative, or other Person who has been Debarred/Excluded.

11.2 **Additional Ionis Representations and Warranties**. Ionis hereby represents and warrants as of the Effective Date to Otsuka that:

11.2.1 It has the right under the Ionis Technology to grant to Otsuka the licenses set forth in this Agreement, and it has not granted any license or other right under the Ionis Technology that is inconsistent with the licenses granted to Otsuka hereunder.

11.2.2 Schedule 1.91 (Ionis Core Technology Patents), Schedule 1.96 (Ionis Manufacturing and Analytical Patents), and Schedule 1.103 (Ionis Product-Specific Patents), collectively, list all Ionis Patent Rights existing as of the Effective Date. With respect to any such Ionis Patent Right identified as being solely owned by Ionis, Ionis owns all rights, title, and interests in and to such Ionis Patent Rights.

11.2.3 As of the Effective Date, all issued Patent Rights within the Ionis Patent Rights are in full force and effect and, to Ionis' Knowledge, are valid and enforceable. To Ionis' Knowledge, all Ionis Patent Rights are being diligently prosecuted in the respective patent offices in the Otsuka Territory in accordance with Applicable Law and have been filed, prosecuted and maintained properly and correctly, and all applicable fees have been paid on or before the due date for payment.

11.2.4 There is no pending or, to Ionis' Knowledge, threatened litigation, nor has Ionis received any written notice from any Third Party, asserting or alleging that the Exploitation of the Licensed Products prior to the Effective Date infringed or misappropriated the Patent Rights, Know-How or other intellectual property rights of such Third Party or that the disclosing, copying, making, assigning, licensing or use of the Ionis Technology infringes or misappropriates any Patent Right, Know-How or other intellectual property rights of such Third Party.

11.2.5 To Ionis' Knowledge, the practice by Otsuka of the Ionis Technology and the Exploitation by Otsuka or its Affiliates or Sublicensee of the Licensed Products in the form existing as of the Effective Date for the treatment of HAE, in each case, does not and will not infringe, misappropriate or otherwise violate any Patent Rights, Know-How or other intellectual property rights of any Third Party.

11.2.6 To Ionis' Knowledge, there are no Third Party Know-How or Patent Rights that are necessary for the Exploitation of Licensed Products in the form existing as of the Effective Date for the treatment of HAE in the Otsuka Territory, other than the Know-How and Patent Rights licensed to Ionis pursuant to the Existing Third-Party IP Agreements. To Ionis' Knowledge, other than the Patent Rights and Know-How licensed to Ionis pursuant to the Existing Third-Party IP Agreements, there are no Third Party Patent Rights that Cover the composition of matter of Licensed Compound or Licensed Products or any Third Party Patent Rights or Know-How that are used in the Manufacture of the Licensed Product in the form existing as of the Effective Date.

11.2.7 There are no pending or, to Ionis' Knowledge, threatened, adverse actions, suits, or proceedings against Ionis involving the Ionis Technology.

11.2.8 To Ionis' Knowledge, no Person is infringing or threatening to infringe or misappropriating or threatening to misappropriate any Ionis Technology in the Otsuka Territory.

11.2.9 There are no legal claims, judgments, or settlements against or owed by Ionis or any of its Affiliates, or pending or, to Ionis' Knowledge, threatened, legal claims or litigation, in each case, relating to antitrust, anti-competition, or anti-corruption law violations.

11.2.10 SCHEDULE 1.49 (Existing Third-Party IP Agreements) sets forth all Existing Third-Party IP Agreements in effect as of the Effective Date, redacted copies of which have been provided to Otsuka prior to the date hereof. Other than the Existing Third-Party IP Agreements set forth in SCHEDULE 1.49 (Existing Third-Party IP Agreements), as of the Effective Date there are no agreements between Ionis and any Third Party pursuant to which Ionis Controls any Know-How or Patent Rights within the Ionis Technology.

11.2.11 Except for Existing Third-Party IP Agreements, Ionis is not obligated under any contract or other agreement with a Third Party as of the Effective Date to make any payments to any owner or licensor of, or other claimant to, any Patent Right, Know-How or other intellectual property or proprietary right with respect to the Exploitation of the Licensed Product in the Otsuka Territory in the form existing as of the Effective Date for the treatment of HAE.

11.2.12 With respect to the Existing Third-Party IP Agreements, Ionis represents and warrants to Otsuka, as of the Effective Date, that: (a) it is in full force and effect; (b) neither Ionis nor any of its Affiliates is in material breach thereof; (c) neither Ionis nor any of its Affiliates has received any notice from any counterparties thereto of any material breach or notice of threatened material breach thereof; (d) neither Ionis nor any of its Affiliates has received any notice from any counterparties thereto of any intent to reduce the scope of the field thereunder or render any of the licenses thereunder non-exclusive or otherwise terminate such Existing Third-Party IP Agreements, and, to Ionis's Knowledge no event, act or omission has occurred which would reasonably give rise to the right of any counterparties thereto to reduce the scope of the field thereof or render any of the licenses thereunder non-exclusive or otherwise terminate such agreement or any licenses thereunder (including with respect to any particular Patent Rights or other intellectual property); (e) neither Ionis nor any of its Affiliates have waived or relinquished any rights thereunder; (f) entering into this Agreement and granting the rights and licenses granted (or purported to be granted) to Otsuka hereunder complies with and will not result in a breach of the terms and conditions of any Existing Third-Party IP Agreement; and (g) Ionis has the right to grant sublicenses to Otsuka under the Existing Third-Party IP Agreements as contemplated herein, including to Develop, Manufacture, Commercialize and conduct Medical Affairs for the Licensed Products in the Field in the Otsuka Territory.

11.2.13 Neither Ionis nor any counterparty to any Existing Third-Party IP Agreement has in writing alleged or threatened that the other party has breached an Existing Third-Party IP Agreement (which has not been cured) or, to Ionis' Knowledge, threatened in writing to terminate an Existing Third-Party IP Agreement.

11.2.14 Each [***].

11.2.15 to Ionis' Knowledge: (a) [***]; and (b) [***].

11.2.16 All preclinical and clinical studies of the Licensed Products sponsored by Ionis or its Affiliates have been and as of the Effective Date are being conducted in material compliance with Applicable Law, including [***]. Neither Ionis 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 Products requiring the termination, suspension, or material modification of such ongoing 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 Products conducted by or on behalf of Ionis or its Affiliates as of the Effective Date.

11.2.17 As of the Effective Date, neither Ionis nor any of its Affiliates, and, to Ionis' Knowledge, none of its or their respective officers, employees, or agents, has made an untrue statement of material fact or fraudulent statement to the FDA or any other Regulatory Authority with respect to the Development of the Licensed Compounds or the Licensed Products, failed to disclose a material fact required to be disclosed to the FDA or any other Regulatory Authority with respect to the Development of the Licensed Compounds or the Licensed Products, or committed an act, made a statement, or failed to make a statement with respect to the Development of the Licensed Compounds or the Licensed Products that could reasonably be expected to provide a basis for the FDA to invoke its policy respecting "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities", set forth in 56 Fed. Reg. 46191 (September 10, 1991) and any amendments thereto or any analogous laws or policies in the Otsuka Territory.

11.2.18 As of the Effective Date, Ionis has no Knowledge of [***] in the Territory in the form existing as of the Effective Date for the treatment of HAE.

11.3 Additional Otsuka Representations and Warranties. Otsuka represents and warrants to Ionis as of the Effective Date that there are no Patent Rights Controlled by Otsuka or any of its Affiliates that are necessary to Exploit a Licensed Product.

11.4 Additional Covenants. Each of Otsuka and Ionis hereby covenant to the other:

11.4.1 **Assignment of Inventions**. Each Party will require all of its and its Affiliates' employees and consultants to assign all Inventions that are developed or invented by such employees according to the ownership principles described in Section 10.1 (Inventions).

11.4.2 **Compliance with Law**. It will, and will ensure that its Affiliates, comply with all Applicable Law and, to the extent applicable, Professional Requirements, with respect to the performance of its obligations under this Agreement, including, as applicable, the Approved Labeling, the European Data Protection Directive 95/46/EC, the European General Data Protection Regulation (Regulation (EU) 2016/679), and any other applicable national data protection legislation.

11.4.3 **No Bribery**. It will not in the future offer, promise, pay, authorize, or give, money or anything of value, directly or indirectly, to any Government Official or Other Covered Party for the purpose, pertaining to this Agreement, of: (a) influencing any act or decision of the Government Official or Other Covered Party; (b) inducing the Government Official or Other Covered Party to do or omit to do an act in violation of a lawful duty; (c) securing any improper advantage; or (d) inducing the Government Official or Other Covered Party to influence the act or decision of a government or government instrumentality, in order to obtain or retain business, or direct business to, any Person, in each case, in any way related to this Agreement.

11.4.4 **Restricted Countries**. Neither it nor its Affiliates will export, transfer, or sell any Licensed Product (a) to any country or territory that is subject to comprehensive economic sanctions administered by OFAC, unless the sale of such Licensed Product would be permissible if Otsuka or its Affiliates or Sublicensees were subject to OFAC's jurisdiction, (b) to any other country or territory in which such activity would violate Applicable Law in the U.S., (c) to any Restricted Party unless the sale of such Licensed Product would be permissible if Otsuka or its Affiliates or Sublicensees was subject to OFAC's jurisdiction, or (d) in such a manner that would violate the Global Trade Control Laws.

11.4.5 **FCPA Compliance**. In performing under this Agreement, it and its Affiliates agree to comply with all applicable anti-corruption laws, including the Foreign Corrupt Practices Act of 1977 and the UK Bribery Act 2010, as amended from time-to-time; the anti-corruption laws of the Territory; and all laws enacted to implement the Organization for Economic Co-operation and Development Convention on Combating Bribery of Foreign Officials in International Business Transactions.

11.4.6 **Debarred/Excluded Persons**. It will not engage, in any capacity in connection with this Agreement or any ancillary agreements, any officer, employee, contractor, consultant, agent, representative, or other Person who has been Debarred/Excluded. Each Party will inform the other Party in writing promptly if it or any Person engaged by it or any of its Affiliates who is performing any obligations under this Agreement or any ancillary agreements is Debarred/Excluded, or if any action, suit, claim, investigation, or legal or administrative proceeding is pending or, to each Party's Knowledge, is threatened, pursuant to which a Party, any of its Affiliates or any such Person performing obligations hereunder or thereunder may become Debarred/Excluded.

11.5 **Disclaimer**. EXCEPT AS EXPRESSLY SET FORTH HEREIN, THE INTELLECTUAL PROPERTY RIGHTS PROVIDED BY EACH PARTY ARE PROVIDED "AS IS" AND WITHOUT WARRANTY. EXCEPT AS EXPRESSLY SET FORTH HEREIN, EACH OF THE PARTIES EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF DESIGN, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, VALIDITY, OR ENFORCEABILITY OF THEIR RESPECTIVE INTELLECTUAL PROPERTY RIGHTS, AND NONINFRINGEMENT OF THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES, ARISING FROM A COURSE OF DEALING, USAGE, OR TRADE PRACTICES, IN ALL CASES WITH RESPECT THERETO.

11.6 **Limitation of Liability**. NEITHER OF THE PARTIES WILL BE ENTITLED TO RECOVER FROM THE OTHER PARTY ANY SPECIAL, INCIDENTAL, INDIRECT, CONSEQUENTIAL, OR PUNITIVE DAMAGES OR DAMAGES FOR LOSS OF PROFIT, LOSS OF REVENUE, OR LOST OPPORTUNITY IN CONNECTION WITH THIS AGREEMENT, ITS PERFORMANCE OR LACK OF PERFORMANCE HEREUNDER, OR ANY LICENSE GRANTED HEREUNDER, EXCEPT TO THE EXTENT THE DAMAGES RESULT FROM A BREACH OF THE OBLIGATIONS OF A PARTY UNDER ARTICLE 12 (CONFIDENTIALITY) OR BREACH OF SECTION 2.5.2 (NEGATIVE COVENANT) BY IONIS, MISAPPROPRIATION OR INFRINGEMENT OF INTELLECTUAL PROPERTY OWNED OR CONTROLLED BY THE OTHER PARTY, OR AMOUNTS REQUIRED TO BE PAID TO A THIRD PARTY AS PART OF A CLAIM FOR WHICH A PARTY PROVIDES INDEMNIFICATION UNDER ARTICLE 13 (INDEMNIFICATION).

ARTICLE 12
CONFIDENTIALITY

12.1 **Duty of Confidence**. Subject to the other provisions of this Article 12 (Confidentiality):

12.1.1 except to the extent expressly authorized by this Agreement, the Receiving Party shall maintain in confidence and otherwise safeguard, and not publish or otherwise disclosed, all Confidential Information of the Disclosing Party;

12.1.2 the Receiving Party will treat all Confidential Information provided by the Disclosing Party, at a minimum, 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;

12.1.3 the Receiving Party may only use any Confidential Information of the Disclosing Party for the purposes of performing its obligations or exercising its rights under this Agreement;

12.1.4 a Receiving Party may only disclose Confidential Information of the Disclosing Party to: (a) such Receiving Party's Affiliates, licensees, and Sublicensees; and (b) employees, directors, officers, agents, contractors, attorneys, accountants and consultants, of the Receiving Party and its Affiliates, licensees, and Sublicensees, in each case ((a) and (b)), to the extent reasonably necessary for the purposes of, and for those matters undertaken pursuant to, this Agreement; *provided* that such Persons are bound by legally enforceable obligations of confidentiality and non-use with respect to the Disclosing Party's Confidential Information, no less stringent than the confidentiality and non-use obligations set forth in this Agreement, except that the term of such obligation will be customary for such recipient of Confidential Information. Each Party will remain responsible for any failure by its Affiliates, licensees, and Sublicensees, and its and its Affiliates', licensees', and Sublicensees' respective employees, directors, officers, agents, consultants, attorneys, accountants and contractors, in each case, to treat such Confidential Information as required under this Section 12.1 (Duty of Confidence) (as if such Persons were Parties directly bound to the requirements of this Section 12.1 (Duty of Confidence)); and

12.1.5 each Party will promptly notify the other Party of any misuse or unauthorized disclosure of the other Party's Confidential Information.

12.1.6 The confidentiality, non-use, and non-disclosure obligations set forth in this Section 12.1 (Duty of Confidence) will be in full force and effect from the Effective Date until [***] after expiration or termination of this Agreement, *provided* that, with respect to any Know-How that is a trade secret and is identified as such by the Disclosing Party at the time of disclosure, the obligations of this Section 12.1 (Duty of Confidence) will continue for so long as such Know-How remains a trade secret.

12.2 **Confidential Information**. Notwithstanding anything to the contrary in the definition of "Confidential Information" set forth in Appendix 1 (Definitions), the Ionis Product-Specific Know-How, any ROFN Exercise Notice, the Joint Collaboration Know-How and the terms of this Agreement will be the Confidential Information of both Parties, with each Party deemed to be the Receiving Party of such information; *provided* that Ionis Product-Specific Know-How will be deemed the Confidential Information of Ionis following any termination (but not expiration) of this Agreement. The Ionis Core Technology Know-How and the Ionis Manufacturing and Analytical Know-How will be the Confidential Information of Ionis. The Otsuka Know-How will be the Confidential Information of Otsuka. Except as provided in Section 12.4 (Authorized Disclosures) and Section 12.6 (Publicity; Use of Names), neither Party nor its Affiliates may disclose the existence or the terms of this Agreement.

12.3 **Exemptions**. Information of a Disclosing Party will not be Confidential Information of such Disclosing Party to the extent that the Receiving Party can demonstrate through competent evidence that such information:

12.3.1 was already known by the Receiving Party or any of its Affiliates without an obligation of confidentiality at the time of its receipt from the Disclosing Party, and not through a prior disclosure by or on behalf of the Disclosing Party, as documented by the Receiving Party's business records;

12.3.2 was generally available to the public or otherwise part of the public domain before its receipt from the Disclosing Party;

12.3.3 became generally available to the public or otherwise part of the public domain after its disclosure by the Disclosing Party other than through any act or omission of the Receiving Party or any of its Affiliates or disclosees in breach of this Agreement;

12.3.4 is subsequently disclosed to the Receiving Party or any of its Affiliates without obligation of confidentiality by a Third Party who may rightfully do so and is not under a conflicting obligation of confidentiality to the Disclosing Party; or

12.3.5 is developed by the Receiving Party or any of its Affiliates independently and without use of or reference to any Confidential Information received from the Disclosing Party, as documented by the Receiving Party's business records.

No combination of features or disclosures will be deemed to fall within the foregoing exclusions merely because individual features are published or available to the general public or in the rightful possession of the Receiving Party unless the combination itself and principle of operation are published or available to the general public or in the rightful possession of the Receiving Party.

12.4 **Authorized Disclosures**.

12.4.1 **Permitted Circumstances**. Notwithstanding the obligations set forth in Section 12.1 (Duty of Confidence), a Party may disclose the other Party's Confidential Information (including this Agreement and the terms herein) to the extent such disclosure is reasonably necessary in the following situations:

(a) the prosecution or enforcement of Ionis Patent Rights, Collaboration Patent Rights, or Otsuka Patent Rights, in each case, as contemplated by this Agreement;

(b) Regulatory Submissions and other filings or communications with Governmental Authorities (including Regulatory Authorities), as necessary for the Exploitation of the Licensed Products in connection with the exercise of the rights and the performance of the obligations of the applicable Party under this Agreement;

(c) disclosure of this Agreement, its terms, and the status and results of Exploitation of the Licensed Products to actual or *bona fide* potential investors, acquirors, (sub)licensees (including any counterparty to a Collaboration In-License), lenders, and other financial or commercial partners (including in connection with any royalty financing transaction), and their respective attorneys, accountants, banks, investors, and advisors, solely for the purpose of evaluating or carrying out an actual or *bona fide* potential investment, acquisition, (sub)license, debt transaction, or collaboration transaction; *provided* that, in each such case, (i) such Persons are bound by obligations of confidentiality and non-use, or subject to professional ethical obligations of confidentiality, at least as stringent as those set forth Article 12 (Confidentiality), except that the term of such obligation will be customary for such recipient of Confidential Information and such type of transaction and (ii) the scope of any such disclosure is limited to the maximum extent practicable for the particular context in which it is being disclosed;

(d) such disclosure is required to comply with Applicable Law (whether generally or in pursuit of an application for listing of securities) including the United States Securities and Exchange Commission or equivalent foreign agency or regulatory body, or otherwise required by judicial or administrative process, *provided* that in each such event, as promptly as reasonably practicable and to the extent not prohibited by Applicable Law or judicial or administrative process, such Party will notify the other Party of such required disclosure and provide a draft of the disclosure to the other Party reasonably in advance of such filing or disclosure for the other Party's review and comment. The non-disclosing Party will provide any comments as soon as practicable, and the disclosing Party will consider in good faith any timely comments provided by the non-disclosing Party; *provided* that the disclosing Party may or may not accept such comments in its reasonable discretion. Confidential Information that is disclosed in order to comply with Applicable Law or by judicial or administrative process pursuant to this Section 12.4.1(d) (Permitted Circumstances), in each case, will remain otherwise subject to the confidentiality and non-use provisions of this Article 12 (Confidentiality) with respect to the Party disclosing such Confidential Information, and such Party will take all steps reasonably necessary, including seeking of confidential treatment or a protective order to the maximum extent permitted by Applicable Law or Governmental Authority, to ensure the continued confidential treatment of such Confidential Information, and each Party will be responsible for its own legal and other external costs in connection with any such filing or disclosure pursuant to this Section 12.4.1(d) (Permitted Circumstances); or

(e) disclosure pursuant to Section 12.6 (Publicity; Use of Names).

(f) If and whenever any Confidential Information is disclosed in accordance with this Section 12.4 (Authorized Disclosures), such disclosure will not cause any such information to cease to be Confidential Information except to the extent that such disclosure results in a public disclosure of such information (other than by breach of this Agreement).

12.5 Publications.

12.5.1 **Otsuka's Right to Publish**. Otsuka will have the right to publicly present or publish any Clinical Trial data, non-clinical or preclinical data, or any associated results or conclusions generated by or on behalf of Ionis or Otsuka pursuant to this Agreement (each such proposed presentation or publication, an "***Otsuka Publication***"), [***]. If Otsuka desires to publicly present or publish an Otsuka Publication in accordance with the foregoing sentence, then Otsuka will provide Ionis (including Ionis' Alliance Manager and all Ionis members of the JSC) with a copy of such proposed Otsuka Publication at least [***] prior to the earlier of its presentation or intended submission for publication (such applicable period, the "***Review Period***"). [***]. Notwithstanding any provision to contrary set forth in this Agreement, Otsuka will [***]. Otsuka will provide Ionis a copy of any Otsuka Publication at the time of the submission or presentation thereof. Otsuka agrees to determine the authorship of all Otsuka Publications in accordance with all applicable International Committee of Medical Journal Editors (ICMJE) guidelines. Otsuka will require its Affiliates and Sublicensees to comply with the obligations of this Section 12.5 (Publications) as if they were Otsuka, and Otsuka will be liable for any non-compliance of such Persons.

12.5.2 **Ionis' Right to Publish**. Ionis will have the right to publicly present or publish any Clinical Trial data, non-clinical or preclinical data, or any associated results or conclusions generated by or on behalf of Ionis pursuant to this Agreement (each such proposed presentation or publication, a "***Ionis Publication***") [***]. If Ionis desires to publicly present or publish a Ionis Publication in accordance with the foregoing sentence, then Ionis will provide Otsuka (including Otsuka's Alliance Manager and all Otsuka members of the JSC) with a copy of such proposed Ionis Publication for review during the applicable Review Period. Ionis [***]. Notwithstanding any provision to contrary set forth in this Agreement, Ionis will [***]. Ionis will provide Otsuka a copy of any Ionis Publication at the time of the submission or presentation thereof. Ionis agrees to determine the authorship of all Ionis Publications in accordance with all applicable International Committee of Medical Journal Editors (ICMJE) guidelines. Ionis will require its Affiliates to comply with the obligations of this Section 12.5 (Publications) as if they were Ionis, and Ionis will be liable for any non-compliance of such Persons.

12.5.3 **Subsequent Publications**. After any Otsuka Publication or Ionis Publication has been published or publicly presented in accordance with Section 12.5.1 (Otsuka's Right to Publish) or Section 12.5.2 (Ionis' Right to Publish), as applicable, either Party may make subsequent publications or presentations of the content of such previously published Otsuka Publication or Ionis Publication without further approval or review by the other Party; *provided*, that such subsequent publication or presentation does not include any new data, information or conclusions, or present the content in a form or manner that materially alters the conclusion or subject matter of the previous publication or public presentation.

12.6 Publicity; Use of Names.

12.6.1 **Press Release**. The Parties may issue a press release announcing this Agreement, on such date and time and in such form, in each case, as may be agreed by the Parties. Other than such press release and the public disclosures permitted by this Section 12.6.1 (Publicity) and Section 12.4 (Authorized Disclosures), the Parties agree that the portions of any other news release or other public announcement relating to this Agreement or the performance hereunder that would disclose information other than that already in the public domain will require prior review and approval by both Parties (with such approval not to be unreasonably withheld, conditioned, or delayed). However, the Parties agree that after (a) a disclosure pursuant to Section 12.6 (Publicity; Use of Names) or Section 12.4 (Authorized Disclosures) or (b) the issuance of a press release (including the initial press release) or other public announcement pursuant to this Section 12.6.1 (Press Release) that has been reviewed and approved by the other Party, the disclosing Party may make subsequent public disclosures reiterating such information without having to obtain the other Party's prior consent and approval so long as the information in such press release or other public announcement remains true, correct, and such disclosure is consistent with prior disclosures approved by the other Party pursuant to this Section 12.6 (Publicity; Use of Names) and which do not reveal non-public information about the other Party. Similarly, after a Publication has been made available to the public, each Party may post such Publication or a link to it on its corporate website or social media platforms (or any website managed by such Party in connection with a Clinical Trial for the Licensed Products, as appropriate) without the prior written consent of the other Party, so long as the information in such Publication remains true, correct, and the most current information with respect to the subject matters set forth therein.

12.6.2 **Disclosures by Ionis**. Notwithstanding any provision to the contrary set forth in this Agreement, Ionis has the right to publicly disclose (in written, oral, or other form): (a) the achievement of any Regulatory Milestone Event or Sales Milestone Event under this Agreement (including the timing of achievement of any such milestone event but without disclosing the amount of such milestone payment unless permitted pursuant to Section 12.4.1(d) (Permitted Circumstances)); (b) the commencement, completion, material data, or key results of any Clinical Trials for the Licensed Products conducted by or on behalf of Ionis; and (c) the achievement of Regulatory Approval for any Licensed Product throughout the world; *provided* that, subject to Section 12.4.1(d) (Permitted Circumstances), [***].

12.6.3 **Use of Names**. Each Party will have the right to use the other Party's name and logo in presentations, its website, collateral materials, and corporate overviews to describe the collaboration relationship, as well as in taglines of press releases issued pursuant to this Section 12.6 (Publicity; Use of Names); *provided* that neither Party will [***], and each Party will [***]. Except as permitted under this Section 12.6 (Publicity; Use of Names) or with the prior express written permission of the other Party, neither Party will use the name, trademark, trade name, or logo of the other Party or its Affiliates or their respective employees in any publicity, promotion, news release, or disclosure relating to this Agreement or its subject matter except as may be required by Applicable Law.

12.7 Acknowledgement.

12.7.1 To the extent permitted under Applicable Law in the Otsuka Territory, Otsuka will acknowledge in any press release, public presentation, or publication regarding a Licensed Product Ionis' role in discovering and developing the Licensed Products, that the Licensed Products are under license from Ionis, and [***].

12.7.2 Otsuka agrees that it will acknowledge Ionis' role in the discovery of a Licensed Product in any scientific, medical, and other Licensed Product-related communications [***], by including the words "*Discovered by Ionis*" or equivalent language (collectively, the "***Ionis Attribution Language***") in any such communications; *provided, however*, that [***].

ARTICLE 13
INDEMNIFICATION

13.1 **Indemnification by Ionis**. Ionis will indemnify, hold harmless, and defend Otsuka and its Affiliates and their respective directors, officers, employees, and agents (each, an "***Otsuka Indemnitee***") from and against any and all Third Party suits, claims, actions, or demands ("***Third Party Claims***") and all liabilities, expenses, or losses (including reasonable attorneys' fees, court costs, witness fees, damages, judgments, fines, and amounts paid in settlement) ("***Losses***") arising therefrom to the extent that the applicable Third Party Claims and such Losses arise out of (a) a breach of this Agreement by Ionis, (b) the Exploitation of the Licensed Products by or on behalf of Ionis or any of its Affiliates, licensees (not including Otsuka or its Affiliates, Sublicensees, or its Subcontractors), Sublicensees, or Subcontractors, or (c) the negligence or willful misconduct of any Ionis Indemnitee. Notwithstanding the foregoing, Ionis will not have any obligation to indemnify Otsuka Indemnitees to the extent that any Losses arise out of any Third Party Claim for which Otsuka is responsible for indemnifying Ionis pursuant to Section 13.2 (Indemnification by Otsuka).

13.2 **Indemnification by Otsuka**. Otsuka will indemnify, hold harmless, and defend Ionis and its Affiliates, and their respective directors, officers, employees, and agents (each, an "***Ionis Indemnitee***") from and against any and all Third Party Claims and all Losses arising therefrom, to the extent that the applicable Third Party Claims and such Losses arise out of (a) a breach of this Agreement by Otsuka, (b) the Exploitation of the Licensed Products by or on behalf of Otsuka or any of its Affiliates, Sublicensees, or Subcontractors, or (c) the negligence or willful misconduct of any Otsuka Indemnitee. Notwithstanding any provision to the contrary set forth in this Agreement, Otsuka will not have any obligation to indemnify the Ionis Indemnitees to the extent that any Losses arise out of any Third Party Claim for which Ionis is responsible for indemnifying Otsuka pursuant to Section 13.1 (Indemnification by Ionis).

13.3 **Indemnification Procedure**. If either Party is seeking indemnification under Section 13.1 (Indemnification by Ionis) or Section 13.2 (Indemnification by Otsuka) (the "***Indemnified Party***"), then it will inform the other Party (the "***Indemnifying Party***") of the Third Party Claim giving rise to such indemnification obligations within [***] after receiving written notice of the Third Party Claim (it being understood and agreed, however, that the failure or delay by an Indemnified Party to give such notice of a Third Party Claim will not affect the Indemnifying Party's indemnification obligations hereunder except to the extent the Indemnifying Party will have been actually prejudiced as a result of such failure or delay to give notice). The Indemnifying Party will have the right to assume the defense of any such Third Party Claim for which it is obligated to indemnify the Indemnified Party. The Indemnified Party will cooperate with the Indemnifying Party and the Indemnifying Party's insurer as the Indemnifying Party may reasonably request, and at the Indemnifying Party's cost and expense. The Indemnified Party will have the right to participate, with counsel of its choice, in the defense of any Third Party that has been assumed by the Indemnifying Party, which participation will be at the Indemnified Party's expense unless (a) the Indemnifying Party has agreed to pay such fees and expenses, or (b) the Indemnified Party has been advised by counsel that there are actual or potential conflicting interests between the Indemnifying Party and the Indemnified Party, including situations in which there are one or more legal defenses available to the Indemnified Party that are different from or additional to those available to the Indemnifying Party. Neither Party will have the obligation to indemnify the other Party in connection with any settlement made without the Indemnifying Party's written consent, which consent will not be unreasonably withheld, conditioned, or delayed. The Indemnifying Party will not admit any fault or negligence on the part of the Indemnified Party, or impose any obligation on, or otherwise adversely affect, the Indemnified Party, without the Indemnified Party's prior written consent, which consent will not be unreasonably withheld, conditioned, or delayed. If the Parties cannot agree as to the application of Section 13.1 (Indemnification by Ionis) or Section 13.2 (Indemnification by Otsuka) as to any Third Party Claim, then, pending resolution of the dispute pursuant to Article 15 (Dispute Resolution; Governing Law), then the Parties may conduct separate defenses of such Third Party Claims, with each Party retaining the right to claim indemnification from the other Party in accordance with Section 13.1 (Indemnification by Ionis) or Section 13.2 (Indemnification by Otsuka), as applicable, upon resolution of the underlying Third Party Claim.

13.4 **Insurance**. Each Party will, at its own expense, procure and maintain insurance, including product liability insurance, adequate to cover its obligations hereunder and that is consistent with normal business practices of prudent companies similarly situated at all times during which any Licensed Product is being clinically tested in human subjects or commercially distributed or sold by such Party pursuant to this Agreement. It is understood that such insurance will not be construed to create a limit of either Party's liability with respect to its indemnification obligations under this Article 13 (Indemnification). Each Party will provide the other Party with written evidence of such insurance upon request. Each Party will provide the other Party with [***].

ARTICLE 14
TERM AND TERMINATION

14.1 **Term**. The term of this Agreement will begin on the Effective Date and, unless earlier terminated in accordance with this Article 14 (Term and Termination), will continue until Otsuka, its Affiliates, and its Sublicensees are no longer Commercializing any Licensed Product in any country in the Otsuka Territory (the "***Term***").

14.2 **Termination for Material Breach**.

14.2.1 **Material Breach**. If either Party believes in good faith that the other is in material breach of this Agreement, then the non-breaching Party may deliver notice of such breach to the other Party stating the cause and proposed remedy ("***Breach Notification***"). For any breach alleged in any Breach Notification arising from a failure to make a payment set forth in this Agreement, the allegedly breaching Party will have [***] from the receipt of the applicable Breach Notification to cure such breach. For all breaches other than a failure to make a payment as set forth in this Agreement, the allegedly breaching Party will have [***] from the date of the Breach Notification to cure such breach. If the allegedly breaching Party fails to cure the applicable breach within the applicable period set forth above, then the Party originally delivering the Breach Notification may terminate this Agreement effective on written notice of termination to such allegedly breaching Party.

14.2.2 **Disagreement as to Material Breach**. Notwithstanding Section 14.2.1 (Material Breach), if the Parties, reasonably and in good faith, disagree as to whether there has been a material breach of this Agreement, then: (a) the Party that disputes whether there has been a material breach may contest the allegation by referring such matter, within the cure period applicable to such alleged material breach, for resolution in accordance with Article 15 (Dispute Resolution; Governing Law); (b) the relevant cure period with respect to such alleged material breach will be tolled from the date on which the Party that disputes whether there has been a material breach notifies the other Party of such dispute and through the resolution of such dispute in accordance with Article 15 (Dispute Resolution; Governing Law); and (c) during the pendency of such dispute, all of the terms and conditions of this Agreement will remain in effect and the Parties will continue to perform all of their respective obligations hereunder.

14.3 **Termination by Otsuka for Convenience**. Otsuka will have the right to terminate this Agreement in its entirety at any time during the Term upon (a) [***] and (b) [***].

14.4 **Discontinuation of Development and Commercialization**. If Otsuka and its Affiliates and Sublicensees have not conducted any material Development or Commercialization activities with respect to the Licensed Products in any country in the Otsuka Territory for a continuous period of [***], and such discontinuation of activity is not: (a) by written agreement of the Parties, (b) due to [***], or (c) due to a Force Majeure, then Ionis may, at its election, terminate this Agreement in its entirety upon [***] prior written notice to Otsuka. For purposes of this Section 14.4 (Discontinuation of Development and Commercialization), the use of reasonable efforts, to the extent possible, by Otsuka or its Affiliates or Sublicensees (as applicable) to resolve a Force Majeure, clinical hold or other action or inaction of a Regulatory Authority, or any scientific or technical issues, Manufacturing or supply interruption or other material adverse event outside of Otsuka's control for the Licensed Product will, in each case, be considered material Development or Commercialization activities.

14.5 **Termination For Patent Challenge**. Except to the extent unenforceable under Applicable Law, Ionis may terminate this Agreement in its entirety upon [***] prior written notice of termination to Otsuka if Otsuka or its Affiliates or Sublicensees (individually or in association with any Person) commences or assists a Third Party in commencing or conducting a Patent Challenge with respect to any Ionis Patent Right, *provided* that, Ionis shall not have the right to terminate this Agreement on account of such Patent Challenge (a) if, within [***] after receipt by Otsuka of the written notice from Ionis as set forth above in this Section 14.5 (Termination for Patent Challenge), Otsuka or its Affiliate, as applicable, rescinds such Patent Challenge (or in the case of any ex-parte proceeding, multi-party proceeding, or other Patent Challenge that Otsuka or such Affiliate does not have the power to unilaterally withdraw or cause to be withdrawn, Otsuka and its Affiliate, as applicable, knowingly ceases providing any direction to any Person with respect to such Patent Challenge and, to the extent Otsuka or any of its Affiliates is a party to such Patent Challenge and to the extent permitted by the applicable tribunal, it withdraws from such Patent Challenge) and *provided* that neither Otsuka nor any of its Affiliates thereafter continues such Patent Challenge or, knowingly provides any direction to any Person in respect of the same or (b) in the case of any Patent Challenge commenced by a Sublicensee of Otsuka or its Affiliate, if Otsuka or its Affiliate, as applicable, terminates such Sublicensee's sublicense under any Ionis Technology within [***] after receipt by Otsuka of the applicable written notice from Ionis as set forth above in this Section 14.5 (Termination for Patent Challenge). If Ionis has the right to terminate this Agreement in accordance with this Section 14.5 (Termination for Patent Challenge) but such termination is prohibited under Applicable Law, then in lieu of such termination, [***]. If Ionis [***], then [***]. Notwithstanding the foregoing, Ionis shall not have the right to terminate this Agreement pursuant to this Section 14.5 (Termination for Patent Challenge) if Otsuka or any of its Affiliates or its or their Sublicensees commences a Patent Challenge (i) in a proceeding involving an Ionis Patent Right in which Otsuka or any of its Affiliates or its or their Sublicensees has been compelled to participate in the proceeding by a court, patent office, or Third Party 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 Otsuka or any of its Affiliates or its or their Sublicensees by Ionis or any of its Affiliates or its or their Sublicensees.

14.6 **Termination for Insolvency**. Each Party will have the right to terminate this Agreement upon delivery of written notice to the other Party if (a) such other Party files in any court or agency pursuant to any statute or regulation of any jurisdiction a petition in bankruptcy or insolvency or for reorganization or similar arrangement for the benefit of creditors or for the appointment of a receiver or trustee of such other Party or its assets, (b) such other Party is served with an involuntary petition against it in any insolvency proceeding and such involuntary petition has not been stayed or dismissed within [***] of its filing, or (c) such other Party makes an assignment of substantially all of its assets for the benefit of its creditors.

14.7 **Rights in Bankruptcy**. 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 Applicable Law. All rights and licenses granted under or pursuant to this Agreement shall be deemed to be "intellectual property" for the purposes of Section 365(n) or any analogous provisions in any other country or jurisdiction. The Parties shall retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code or any analogous provisions in any other country or jurisdiction, 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 analogous provisions in any other country or jurisdiction, the Party that is not subject to such proceeding shall be entitled to a complete duplicate of (or complete access to, as appropriate) all such intellectual property (including all embodiments of such intellectual property), which, if not already in the non-subject Party's possession, shall be promptly delivered to it upon the non-subject Party's 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.

14.8 **Full Force and Effect During Notice Period**. This Agreement will remain in full force and effect until the expiration of the applicable termination notice period. For clarity, if Otsuka or any of its Affiliates or Sublicensees achieve any Milestone Events during the termination notice period, then the corresponding Milestone Payment is accrued and Otsuka will remain responsible for the payment of such Milestone Payment even if the due date of such Milestone Payment occurs after the effective date of the termination.

14.9 **Effects of Termination**. If this Agreement is terminated by either Party pursuant to Section 14.2 (Termination for Material Breach) or Section 14.6 (Termination for Insolvency), by Otsuka pursuant to Section 14.3 (Termination by Otsuka for Convenience), or by Ionis pursuant to Section 14.4 (Discontinuation of Development and Commercialization), or Section 14.5 (Termination for Patent Challenge), then all rights in the Licensed Products will revert to Ionis, and the following will apply with respect to the Licensed Products:

14.9.1 **Termination of Licenses**. As of the effective date of termination of this Agreement, all rights licensed to Otsuka under Section 2.1 (License Grants to Otsuka) or otherwise under this Agreement (except for the licenses granted under Section 2.4 (Collaboration Technology Enabling License)), in each case, will each terminate, but each Party will retain its joint ownership interests in the Joint Collaboration Technology.

14.9.2 **Reversion License**.

(a) **License Grant**. Ionis will have, and Otsuka hereby grants to Ionis, effective upon such termination, a worldwide, [***] license under any Patent Rights and Know-How Controlled by Otsuka as of the effective date of such termination, other than any Otsuka Technology, that, in each case, are used by Otsuka or its Affiliates in the Exploitation of any Licensed Product prior to or as of the effective date of such termination solely to Exploit the Licensed Products in the Territory (the "***Reversion License***"). Except as otherwise provided in Section 14.9.8 (Sell-Off), Otsuka will not have the right to Commercialize any Licensed Product in the Territory upon and following the effective date of termination of this Agreement.

(b) **Reversion Royalty**. Ionis will pay, on a Calendar Quarter basis during the applicable Royalty Term (defined *mutatis mutandis* with respect to the Reversion License except that, for clarity, references to the Ionis Patent Rights in such definition will instead refer to any Patent Rights licensed by Otsuka to Ionis under the Reversion License) a [***] royalty on Ionis' Net Sales (defined *mutatis mutandis* with respect to the Reversion License) of each Licensed Product in the Territory. The provisions of Section 9.3.4 (Royalty Payments and Reports) through Section 9.11 (Late Payments; Disputed Payments) will apply to such payment obligation *mutatis mutandis*. Notwithstanding the foregoing, in no event will the total amount of the reversion royalty payments under this Section 14.9.2(b) (Reversion Royalty) exceed [***].

14.9.3 **Transition Services**.

(a) **Scope**. Ionis may request that Otsuka perform transition activities with respect to any Licensed Products in the Otsuka Territory that are necessary to transition the responsibilities under all Regulatory Approvals and ongoing Clinical Trials for Licensed Products to Ionis or its designee. If Ionis requests that Otsuka perform any such transition activities, then the Parties will enter into a transition agreement containing a plan for Otsuka to perform the transition services listed in SCHEDULE 14.9.3 (Transition Services), to the extent applicable at the time of termination, and such other transition services that the Parties mutually agree to (such plan, the "***Transition Plan***" and such activities, the "***Transition Services***").

(b) **Transition Plan**. Ionis may elect to have Otsuka perform the Transition Services by providing written notice to Otsuka no later than [***] following the effective date of the termination. If Ionis requests that Otsuka perform the Transition Services, then Ionis will propose a draft of the Transition Plan setting forth the Transition Services to be performed by Otsuka and the Parties will negotiate and enter into the Transition Plan, which will be consistent with this Section 14.9.3 (Transition Services) and will include, to the extent applicable, the services listed on SCHEDULE 14.9.3 (Transition Services), within [***] after such request. 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 Otsuka is providing Transition Services, Otsuka and Ionis will mutually agree on talking points and a communication plan to customers, specialty pharmacies, physicians, Regulatory Authorities, patient advocacy groups, and clinical study investigators, and Otsuka will make all such communication to such entities in accordance with the mutually agreed talking points.

(c) **Costs**. Ionis will pay Otsuka for [***]. In addition, Ionis will reimburse Otsuka for [***]. Otsuka will submit an invoice, together with supporting documentation of [***], to Ionis quarterly for the foregoing costs incurred by or on behalf of Otsuka in such Calendar Quarter, and Ionis will pay the undisputed invoiced amounts within [***] after the date of such invoice (and will pay any disputed amounts within [***] following resolution of the dispute and determination that such amounts are owed).

14.9.4 **Return of Confidential Information**. Each Party will return or destroy (at the other Party's election) all Confidential Information of the other Party in its possession upon termination of this Agreement and, if applicable, the Receiving Party will provide a written confirmation of such destruction within [***] of such request. Notwithstanding the foregoing or any provision to the contrary set forth in this Agreement: (a) the foregoing terms of this Section 14.9.4 (Return of Confidential Information) will not apply to any Confidential Information that is necessary to allow the Receiving Party to perform its obligations or exercise any of its rights that expressly survive the applicable termination of this Agreement, and the Receiving Party may retain one copy of such Confidential Information for its legal archives; and (b) the Receiving Party will not be required to destroy electronic files containing such Confidential Information that are made in the ordinary course of its business information back-up procedures pursuant to its electronic record retention and destruction practices that apply to its own general electronic files and information.

14.9.5 **Sublicenses**. If this Agreement is terminated prior to expiration, then Ionis shall grant to each Sublicensee of Otsuka, at each such Sublicensee's written request to Ionis within [***] of the effective date of termination, a direct license, *provided* that such Sublicensee (a) is not then in default of its sublicense agreement or this Agreement, (b) agrees in writing to comply with the terms of this Agreement to the extent applicable to the rights originally sublicensed to such Sublicensee by Otsuka, and (c) agrees to pay directly to Ionis such Sublicensee's payments under such sublicense agreement. The scope of such direct license shall be no less than the scope of the license granted herein and sublicensed to such Sublicensee, and Ionis shall have no obligation to perform any task for such Sublicensee beyond the obligations owed to Otsuka hereunder. Each Sublicensee will be an intended Third Party beneficiary of this Section 14.9.5 (Sublicenses) with the right to enforce the same against Ionis.

14.9.6 **Assignment**. To the extent requested by Ionis in writing following the date that a Party provides notice of termination of this Agreement, Otsuka will promptly (and in any event no later than [***] after the effective date of termination unless agreed otherwise in the Transition Plan or expressly specified otherwise below):

(a) provide to Ionis for its review unredacted copies of all clinical trial agreements and distribution agreements (to the extent assignable, not cancelled, and solely related to the Licensed Products), in each case, that are necessary or reasonably useful for the Exploitation of the Licensed Products, and, following such review, upon Ionis' written request within [***] after entering into a Transition Plan or [***] after the effective date of termination if Ionis does not elect to enter into a Transition Plan, assign and transfer to Ionis or its designee all of Otsuka's rights, title, and interests in and to any such agreements;

(b) assign to Ionis any Potential In-Licenses entered into by Otsuka pursuant to Section 2.7.2 (Potential In-Licenses);

(c) assign any agreements or arrangements with Third Party vendors (including distributors) solely related to the Licensed Products or, to the extent any such Third Party agreement or arrangement is not assignable to Ionis, reasonably cooperate with Ionis to arrange to continue to provide such services for a reasonable time after termination of this Agreement to facilitate the orderly transition of all Commercialization and other activities then being performed by or on behalf of Otsuka or its Affiliates or Sublicensees for the Licensed Products to Ionis or its designee;

(d) assign and transfer to Ionis or its designee, as of the effective date of termination, all of Otsuka's rights, title, and interests in and to the Otsuka Product Trademarks and any domain names associated with the Otsuka Product Trademarks (to the extent that Otsuka or its Affiliates has any) and promptly provide to Ionis all information necessary to maintain such domain names;

(e) assign and transfer to Ionis or its designee, as of the effective date of termination, all of Otsuka's rights, title, and interests in and to any Product Materials specifically related to the Licensed Products, and copyrights and any registrations for the foregoing (to the extent that Otsuka or its Affiliates has any); and

(f) within [***] after entering into a Transition Plan or [***] after the effective date of termination if Ionis does not elect to enter into a Transition Plan, disclose to Ionis or its designee all documents, records, and materials that embody any of the foregoing and that are Controlled by Otsuka.

To the extent that any agreement or other asset described in this Section 14.9.6 (Assignment) is not assignable by Otsuka, then such agreement or other asset will not be assigned, and upon the request of Ionis, Otsuka will take such steps as may be necessary to allow Ionis to obtain and to enjoy the benefits of such agreement or other asset, in the form of a license or other right to the extent Otsuka has the right and ability to do so; *provided* that such steps will not require Otsuka to [***] in order to obtain and enjoy such benefits. For clarity, Ionis will have the right to request that Otsuka take any or all of the foregoing actions in whole or in part, or with respect to all or any portion of the assets set forth in the foregoing provisions.

14.9.7 **Regulatory Submissions and Regulatory Approvals**. Otsuka will and hereby does, and will cause its Affiliates and Sublicensees to, (a) no later than [***] after the effective date of termination of this Agreement, assign and transfer to Ionis or its designee all of Otsuka's rights, title, and interests in and to all Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals solely for the Licensed Products then Controlled by Otsuka or any of its Affiliates or Sublicensees (for any Sublicensees that do not become a direct licensee of Ionis pursuant to Section 14.9.5 (Sublicenses)), and (b) to the extent assignment pursuant to clause (a) is delayed or is not permitted by the applicable Regulatory Authority, permit Ionis to cross-reference and rely upon any such Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals filed by Otsuka or any of its Affiliates or Sublicensees (for any Sublicensees that do not become a direct licensee of Ionis pursuant to Section 14.9.5 (Sublicenses)). Otsuka will execute and deliver, or will cause to be executed and delivered, to Ionis or its designee such endorsements, assignments, commitments, acknowledgements, and other documents as may be necessary to effect the foregoing assignment, including submitting to each applicable Regulatory Authority or other Governmental Authority a letter or other necessary documentation (with copy to Ionis) notifying such Regulatory Authority or other Governmental Authority of, or otherwise giving effect to, the transfer of ownership to Ionis of all such assigned Regulatory Submissions, Regulatory Approvals, and Reimbursement Approvals. In addition, upon Ionis' written request, Otsuka will, [***] (other than in the event of termination of this Agreement by Otsuka pursuant to Section 14.2 (Termination for Material Breach) or Section 14.6 (Termination for Insolvency), in which case Ionis shall [***]), provide to Ionis copies of all material related documentation, including material non-clinical, preclinical, and clinical data related to the Licensed Products that are held by or reasonably available to Otsuka or its Affiliates or Sublicensees (for any Sublicensees that do not become a direct licensee of Ionis pursuant to Section 14.9.5 (Sublicenses)).

14.9.8 **Sell-Off**. If Otsuka is Commercializing any Licensed Product in any country in the Otsuka Territory as of the applicable effective date of termination, then, [***], either (a) Otsuka will appoint Ionis or its designee as its exclusive distributor of such Licensed Product in such country and grant Ionis or its designee the right to appoint sub-distributors, to the extent not prohibited by any written agreement between Otsuka or any of its Affiliates and a Third Party or (b) Otsuka will have the continued right to sell the Licensed Products in the Otsuka Territory from its inventory; *provided*, *however*, that Otsuka's obligations under this Agreement with respect to the Licensed Products that Otsuka sells, including the obligation to pay Royalties to Ionis hereunder, will continue in full force and effect during such period. If Ionis elects to be appointed as the exclusive distributor pursuant to the foregoing clause (a), then the Parties will enter into a distribution agreement with respect to such appointment and Ionis will use good faith efforts to distribute such Licensed Product in such country, or otherwise distribute such Licensed Product in such country, in accordance with the terms of the distribution agreement.

14.9.9 **Inventory**. [***].

14.9.10 **Wind Down and Transition**. Otsuka will be responsible, [***] (other than in the event of termination of this Agreement by Otsuka pursuant to Section 14.2 (Termination for Material Breach) or Section 14.6 (Termination for Insolvency), in which case Ionis shall [***]), for the wind-down of Otsuka's and its Affiliates' and Sublicensees (for any Sublicensees that do not become a direct licensee of Ionis pursuant to Section 14.9.5 (Sublicenses)) activities with respect to the Licensed Products. Otsuka will, and will cause its Affiliates and such Sublicensees to, reasonably cooperate with Ionis to facilitate orderly transition to Ionis or its designee of all Commercialization and other activities then being performed by or on behalf of Otsuka or its Affiliates for the Licensed Products in the Otsuka Territory.

14.9.11 **Cost of Transition Activities**. Notwithstanding any provision to the contrary in this Section 14.9 (Effects of Termination), but without limiting Section 14.9.3(c) (Costs), if Otsuka terminates this Agreement pursuant to Section 14.2 (Termination for Material Breach) or Section 14.6 (Termination for Insolvency), Ionis will be responsible for, and will pay Otsuka, [***]. Otsuka will submit an invoice, together with supporting documentation of [***], to Ionis quarterly for the foregoing costs incurred by or on behalf of Otsuka in such Calendar Quarter, and Ionis will pay the undisputed invoiced amounts within [***] after the date of any such invoice (and will pay any disputed amounts within [***] following resolution of the dispute and determination that such amounts are owed).

14.9.12 **Other Assistance; Further Assurances**. Otsuka will provide any other assistance reasonably requested by Ionis for the purpose of allowing Ionis or its designee to proceed expeditiously with the Exploitation of the Licensed Products for a period of [***] after the effective date of termination of this Agreement. Otsuka will execute all documents, and take all such further actions as may be reasonably requested by Ionis in order to give effect to the requirements in this Section 14.9 (Effects of Termination).

14.10 Survival; Accrued Rights. Expiration or termination of this Agreement will not relieve the Parties of any liability that accrued hereunder prior to the effective date of such expiration or termination nor preclude either Party from pursuing all rights and remedies it may have hereunder or at law or in equity with respect to any breach of this Agreement, nor prejudice either Party's right to obtain performance of any obligation. Without limiting the foregoing, the following provisions of this Agreement will survive the expiration or termination of this Agreement: Section 2.2 (License Grant to Ionis); Section 2.4 (Collaboration Technology Enabling License); Section 4.6 (Development Records; Cooperation) (solely with respect to the obligation to maintain records for at least [***] after the end of the Term or for such longer period as may be required by Applicable Law); Article 9 (Payments) (solely with respect to amounts that accrued prior to the effective date of termination and, with respect to Section 9.5 (Financial Records and Audits), solely for [***] after the effective date of termination), Section 10.1 (Inventions); Section 11.5 (Disclaimer); Section 11.6 (Limitation of Liability); Article 12 (Confidentiality, excluding Section 12.5 (Publications)); Article 13 (Indemnification); Section 14.9 (Effects of Termination); this Section 14.10 (Survival; Accrued Rights); Article 15 (Dispute Resolution; Governing Law); Article 16 (Miscellaneous); and Appendix 1 (Definitions).

ARTICLE 15
DISPUTE RESOLUTION; GOVERNING LAW

15.1 Executive Officers; Disputes. Each Party will ensure that an Executive Officer is designated for such Party at all times during the Term for dispute resolution purposes, and will promptly notify the other Party of any change in its designated Executive Officer. In the event of a dispute, controversy or claim arising under, relating to, or in connection with this Agreement (except for disputes arising at the JSC, which will be resolved in accordance with Section 8.4 (Decision-Making) and Section 8.5 (Resolution of Committee Disputes)) (a "***Disputed Matter***"), then the Parties will refer such dispute to their respective Executive Officer, and such Executive Officers or designees will attempt in good faith to resolve such dispute. If the Parties are unable to resolve any such dispute within [***] after both Parties have referred such dispute to their designated Executive Officers pursuant to this Section 15.1 (Executive Officers; Disputes), then either Party will have the right to pursue any and all remedies available at law or equity, as set forth in Section 15.2 (Arbitration) or Section 15.3 (Intellectual Property Disputes), as applicable.

15.2 Arbitration.

15.2.1 If the Parties are unable to resolve a Disputed Matter using the process described in Section 15.1 (Executive Officers; Disputes) and Section 15.3 (Intellectual Property Disputes) does not apply, then a Party seeking further resolution of the Disputed Matter will submit the Disputed Matter to resolution by final and binding arbitration in accordance with this Section 15.2 (Arbitration).

15.2.2 The seat, or legal place, of arbitration will be New York, New York. The arbitration will be administered by the International Chamber of Commerce pursuant to its Rules of Arbitration in effect at the time of the arbitration, (the "***Rules***"), except they may be modified as set forth herein, and applying the substantive law specified in Section 15.5 (Governing Law; English Language). The language of the arbitration will be English.

15.2.3 Unless a Party elects for application of the ICC's Expedited Procedure Rules pursuant to Section 15.2.4 (Arbitration) or the Expedited Procedure Rules otherwise apply because of the amount in dispute, the arbitration will be conducted by a tribunal of three arbitrators. The claimant will nominate an arbitrator in its request for arbitration; the respondent will nominate an arbitrator within [***] of receipt of the request for arbitration; and the two-party nominated arbitrators will nominate the third, who will serve as chair of the tribunal, within [***] of the second arbitrator's appointment. If any of the three arbitrators are not nominated within the time prescribed above, then the ICC will appoint the arbitrator(s). Within [***] of the commencement of arbitration, the Parties will attempt in good faith to reach agreement upon and thereafter follow procedures directed at assuring that the arbitration will be concluded and the award rendered within no more than [***] from the date the ICC Secretariat transmits the file to the arbitral tribunal. Failing such agreement, the arbitral tribunal will design and the Parties will follow procedures directed at meeting such a time schedule. Each arbitrator must have at least [***] of business or legal experience in the pharmaceutical industry. An arbitrator will be deemed to meet these qualifications unless a Party objects within [***] after the arbitrator is nominated.

15.2.4 Notwithstanding Section 15.2.3 (Arbitration), if the Disputed Matter involves the dispute of a Breach Notification for any default other than a determination of an alleged failure to use Commercially Reasonable Efforts to Develop or Commercialize the Licensed Product, the non-breaching Party may elect on notice to the breaching Party to apply the ICC Expedited Procedure Rules to the arbitration and, if such election is made, the number of arbitrators will be one and the period for the rendering of the final award will be [***] from the date of the case management conference.

15.2.5 The Parties agree that any dispute concerning the propriety of the commencement of the arbitration or the scope and applicability of the agreement to arbitrate will be determined by the arbitrator(s).

15.2.6 No tribunal of arbitrators will have the power to award damages excluded pursuant to Section 11.6 (Limitation of Liability).

15.2.7 Article 38 of the Rules will apply with respect to the costs of the arbitration.

15.2.8 Except as may be required by Applicable Law, neither a Party nor any arbitrator may disclose the existence, content or results of any arbitration hereunder without the prior written consent of both Parties, unless to protect or pursue a legal right. The arbitral award will be final and binding on the Parties and the Parties will carry out the award without delay. Judgment on the award so rendered may be entered in any court of competent jurisdiction. No award or procedural order made in the arbitration shall be published.

15.3 Intellectual Property Disputes. Notwithstanding any provision to the contrary set forth in this Agreement, if a dispute arises under this Agreement with respect to the validity, scope, enforceability, or ownership of any Patent Right or other intellectual property rights, and such dispute is not resolved in accordance with Section 15.1 (Executive Officers; Disputes), then such dispute will be submitted to a court of competent jurisdiction in the jurisdiction in which such Patent Right or other intellectual property right was granted or arose.

15.4 **Equitable Remedies**. Notwithstanding any provision to the contrary set forth in this Agreement, the Parties each stipulate and agree that (a) the other Party's Confidential Information includes highly sensitive trade secret information such that a breach of Article 12 (Confidentiality) by a Party will cause irrevocable harm for which monetary damages would not provide a sufficient remedy; and (b) in such case of such breach of Article 12 (Confidentiality), the non-breaching Party will be entitled to seek equitable relief, including specific performance, temporary or permanent restraining orders, preliminary injunction, permanent injunction, or other equitable relief without the posting of any bond or other security. In addition, and notwithstanding any provision to the contrary set forth in this Agreement, in the event of any other actual or threatened breach hereunder, the aggrieved Party may seek interim equitable relief (including temporary restraining orders, or other provisional equitable relief) from any court of competent jurisdiction without first submitting to the dispute resolution procedures set forth in Article 15 (Dispute Resolution; Governing Law) and shall retain that right after the appointment of the arbitrator(s).

15.5 **Governing Law; English Language**. This Agreement and all amendments, modifications, alterations, or supplements hereto, and the rights of the Parties, will be construed under and governed by the laws of the State of New York, United States, exclusive of its conflicts of laws principles. This Agreement has been prepared in the English language and the English language will control its interpretation. All consents, notices, reports, and other written documents to be delivered or provided by a Party under this Agreement will be in the English language, and in the event of any conflict between the provisions of any document and the English language translation thereof, the terms of the English language translation will control.

ARTICLE 16
MISCELLANEOUS

16.1 **Assignment**. This Agreement may not be assigned or otherwise transferred, nor may any right or obligation hereunder be assigned or transferred, by either Party without the prior written consent of the other Party. Notwithstanding the foregoing, (a) Ionis may assign its rights to receive payments under this Agreement to one or more Persons (including as part of a royalty monetization transaction) (a "***Payment Assignment***") without consent of Otsuka; *provided* that Ionis shall give prompt written notice to Otsuka upon making a Payment Assignment, and any assignee of a Payment Assignment shall not have any rights, including any audit rights, hereunder (other than the right to receive payments under this Agreement) unless Otsuka provides express prior written consent, which Otsuka may grant or withhold in its discretion, and (b) either Party may, without consent of the other Party, assign this Agreement and its rights and obligations hereunder (i) in whole or in part to an Affiliate of such Party (for so long as such Affiliate remains an Affiliate), or (ii) in whole to its successor-in-interest in connection with the sale of all or substantially all of its assets, whether in a merger, acquisition, or similar transaction or series of related transactions. If there is an assignment pursuant to the foregoing clauses (b)(i) or (b)(ii), then such assignment will only be effective if the Person to whom this Agreement is assigned agrees in writing to assume all of the assigning Party's obligations under this Agreement and the assigning Party provides written notice of such assignment to the non-assigning Party within [***] after the effective date of such assignment. Any attempted assignment of this Agreement in violation of this Section 16.1 (Assignment) will be null, void, and of no legal effect. Any permitted assignee will assume all assigned obligations of its assignor under this Agreement. This Agreement will be binding on and will inure to the benefit of the permitted successors and assigns of the Parties.

16.2 **Entire Agreement; Amendment**. This Agreement and the Ancillary Agreements, together with all exhibits and schedules attached hereto, constitutes the entire agreement between the Parties with respect to the subject matter hereof, and supersedes and merges all prior and contemporaneous negotiations, representations, and understandings regarding the same, (including that certain mutual confidential disclosure agreement between the Parties dated [***] ("***Confidential Disclosure Agreement***")). All information shared by the Parties pursuant to the Confidential Disclosure Agreement will be Confidential Information under this Agreement from and after the Effective Date, and the use and disclosure thereof will be governed by Article 12 (Confidentiality). This Agreement may not be modified or amended, except by another agreement in writing executed by duly authorized signatories of each Party.

16.3 **No Strict Construction; Interpretation**. This Agreement has been prepared jointly and will not be strictly construed against either Party. Ambiguities, if any, in this Agreement will not be construed against any Party, irrespective of which Party may be deemed to have authored the ambiguous provision. Except where the context expressly requires otherwise, (a) whenever any provision of this Agreement uses the term "including" (or "includes"), such term will be deemed to mean "including without limitation" and "including but not limited to" (or "includes without limitations" and "includes but is not limited to") regardless of whether the words "without limitation" or "but not limited to" actually follow the term "including" (or "includes"); (b) "herein," "hereby," "hereunder," "hereof," and other equivalent words will refer to this Agreement in its entirety and not solely to the particular portion of this Agreement in which any such word is used; (c) all definitions set forth herein will be deemed applicable whether the words defined are used herein in the singular or the plural; (d) wherever used herein, any pronoun or pronouns will be deemed to include both the singular and plural and to cover all genders; (e) the schedules and exhibits to this Agreement, and the terms and conditions incorporated in such schedules and exhibits will be deemed integral parts of this Agreement and all references in this Agreement to this Agreement will encompass such schedules and exhibits and the terms and conditions incorporated in such schedules and exhibits; *provided* that if there is a conflict between the terms and conditions of this Agreement and any terms and conditions set forth in the schedules, or exhibits, then the terms of this Agreement will control; (f) in the event of any conflict between the terms and conditions of this Agreement and any terms and conditions that may be set forth on any order, invoice, or verbal agreement by the Parties pursuant to this Agreement, the terms and conditions of this Agreement will govern; (g) unless otherwise provided, all references to Sections, Articles, and Schedules in this Agreement are to Sections, Articles, and Schedules of and to this Agreement; (h) any reference to any federal, national, state, local, or foreign statute or law will be deemed to also refer to all rules and regulations promulgated thereunder, and any reference to any law, rule, or regulation will be deemed to include the then-current amendments thereto or any replacement or successor law, rule, or regulation thereof; (i) wherever used, the word "shall" and the word "will" are each understood to be imperative or mandatory in nature and are interchangeable with one another; (j) the term "or" will be interpreted in the inclusive sense commonly associated with the term "and/or"; (k) references to a particular Person include such Person's successors and assigns to the extent not prohibited by this Agreement; (l) the section headings and captions used herein are inserted for convenience of reference only and will not be construed to create obligations, benefits, or limitations; (m) any definition of or reference to any agreement, instrument, or other document herein will be construed as referring to such agreement, instrument, or 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); (n) the word "notice" means notice in writing (whether or not specifically stated) and will include notices, consents, approvals, and other written communications contemplated under this Agreement; and (o) provisions that require that a Party, the Parties, or any committee hereunder "agree," "consent," or "approve" or the like will require that such agreement, consent, or approval be specific and in writing, whether by written agreement, letter, approved minutes, or otherwise (but excluding email and instant messaging).

16.4 **Severability**. If any provision of this Agreement is declared invalid by a court of last resort or by any court or other governmental body the decision of which an appeal is not taken within the time provided by law, then and in such event, this Agreement will be deemed to have been terminated only as to the portion thereof that relates to the provision invalidated by that decision and only in the relevant jurisdiction, but this Agreement will remain in force, in all other respects and all other jurisdictions; *provided, however*, that if the provision so invalidated is essential to this Agreement as a whole, then the Parties will negotiate in good faith to amend the terms hereof as nearly as practical to carry out the original intent of the Parties, and, failing such amendment, either Party may submit the matter for resolution pursuant to Article 15 (Dispute Resolution; Governing Law).

16.5 **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 of this Agreement when such failure or delay is due to Force Majeure. For purposes of this Agreement, "***Force Majeure***" is defined as any cause beyond the control of the affected Party and without the fault or negligence of such Party, which may include acts of God; material changes in Applicable 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. Notwithstanding the foregoing, a Party will not be excused from making payments owed hereunder due to any such Force Majeure circumstances affecting such Party. The Party affected by 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 [***], 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 this Agreement. To the extent possible, each Party will use reasonable efforts to minimize the duration of any Force Majeure.

16.6 **Notices**. All notices that are required or permitted hereunder will be in writing and sufficient if delivered by internationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, and in each case, addressed as follows (with a courtesy copy sent by email, which will not constitute notice):

If to Ionis:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Attention: Chief Business Officer

With a copy (which will not constitute notice for purposes of this Ag*reement) to each of*:

[***]
Attention: General Counsel

If to Otsuka:

Otsuka Pharmaceutical Co., Ltd.
Shinagawa Grand Central Tower
2-16-4 Konan, Minato-ku
Tokyo, 108-8242 Japan
Attn: Director, Global Business Development
Email: [***]

With a copy (which will not constitute notice for purposes of this Agreement) to:

Otsuka Pharmaceutical Co., Ltd.
Shinagawa Grand Central Tower
2-16-4 Konan, Minato-ku
Tokyo, 108-8242 Japan
Attn: Director, Legal Affairs Department
Email: [***]

Otsuka Pharmaceutical Europe Ltd.
2 Windsor Dials, Arthur Road,
Windsor, SL4 1RS, United Kingdom
Attn: General Counsel
Email: [***]

or to such other address as the Party to whom notice is to be given may have furnished to the other Party in writing in accordance herewith. Any such notice will be deemed to have been given: (a) on the Business Day after dispatch if sent by internationally-recognized overnight courier; or (b) on the fifth Business Day after dispatch if sent by registered or certified mail, postage prepaid, return receipt requested.

16.7 **Further Assurances**. The Parties agree to reasonably cooperate with each other in connection with any actions required to be taken as part of their respective obligations under this Agreement, and will (a) furnish to each other such further information; (b) execute and deliver to each other such other documents; and (c) do such other acts and things (including working collaboratively to correct any clerical, typographical, or other similar errors in this Agreement), all as the other Party may reasonably request for the purpose of carrying out the intent of this Agreement.

16.8 **Performance by Affiliates**. Notwithstanding any provision to the contrary set forth in this Agreement, either 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 Affiliate. 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.

16.9 **Agency**. Neither Party is, nor will be deemed to be an employee, agent, or representative of the other Party for any purpose. Each Party is an independent contractor, not an employee or partner of the other Party. Neither Party will have the authority to speak for, represent, or obligate the other Party in any way without prior written authority from the other Party.

16.10 **Binding Effect; No Third-Party Beneficiaries or Obligors**. As of the Effective Date, this Agreement will be binding upon and inure to the benefit of the Parties and their respective permitted successors and assigns. Except as set forth in Article 13 (Indemnification), no Person other than Ionis, Otsuka, and their respective permitted successors and assigns hereunder will be deemed an intended beneficiary hereunder, nor have any right to enforce any obligation of any Party to this Agreement, nor will any Person other than Ionis and Otsuka and their respective permitted successors and assigns have any obligations to any Party under this Agreement.

16.11 **No Waiver**. Any omission or delay by either Party at any time to enforce any right or remedy reserved to it, or to require performance of any of the terms, covenants, or provisions hereof, by the other Party, will not constitute a waiver of such Party's rights to the future enforcement of its rights under this Agreement. Any waiver by a Party of a particular breach or default by the other Party will not operate or be construed as a waiver of any subsequent breach or default by the other Party.

16.12 **Cumulative Remedies**. No remedy referred to in this Agreement, including termination of this Agreement, is intended to be exclusive, but each will be cumulative and in addition to any other remedy referred to in this Agreement or otherwise available under law.

16.13 **Counterparts**. This Agreement may be executed in one or more counterparts, all of which taken together will be regarded as one and the same instrument. Each Party may execute this Agreement in Adobe™ Portable Document Format (PDF) sent by electronic mail. PDF signatures of authorized signatories of the Parties will be deemed to be original signatures, will be valid and binding upon the Parties, and, upon delivery, will constitute due execution of this Agreement.

[Remainder of page intentionally left blank; Signature page follows.]

IN WITNESS WHEREOF, the Parties have executed this Agreement through their duly authorized representatives to be effective as of the Effective Date.

IONIS PHARMACEUTICALS, INC.

By: */s/ Brett Monia, PhD*
Name: Brett Monia, PhD
Title: Chief Executive Officer

Otsuka Pharmaceutical Co., Ltd.

By: */s/ Makoto Inoue*
Name: Makoto Inoue
Title: President and Representative Director

Otsuka Pharmaceutical Co., Ltd.

By: */s/ Takeshi Watanabe*
Name: Takeshi Watanabe, PhD, MBA
Title: VP, Global Head of Business Development

[Signature Page to License Agreement]

Appendix 1

Definitions

For purposes of this Agreement, whether used in the singular or plural, the following terms will have the meanings set forth below:

1.1 "***Accounting Standards***" means, with respect to a Party or its Affiliate or Sublicensee, GAAP or IFRS, as such Person uses for its financial reporting standards from time to time, in each case, as consistently applied.

1.2 "***Affiliate***" means, with respect to a Person, any corporation or other business entity controlled by, controlling, or under common control with such Person, with "control" meaning (a) direct or indirect beneficial ownership of more than 50% of the voting stock or other ownership interest of, or more than 50% interest in the income of, the applicable entity, or (b) the possession, directly or indirectly, of the power to direct the management or policies of the applicable entity, whether through the ownership of voting securities or other equity rights, by contract relating to voting rights or corporate governance, or otherwise. Notwithstanding the foregoing, for purposes of this Agreement, "Affiliates" will not include, (a) with respect to an entity, *bona fide* venture capital investors in such entity or *bona fide* institutional investors in such entity, in each case, that routinely make venture capital investments for the potential financial return on such investments and not with any view to acquisition or for other strategic purpose, or Affiliates of such venture capital or institutional investors, or (b) with respect to Otsuka, any entities that are controlled by Otsuka Holdings Co., Ltd. but are not subsidiaries of Otsuka.

1.3 "***Alliance Manager***" has the meaning set forth in Section 8.7 (Alliance Managers).

1.4 "[***]" means any [***].

1.5 "***Ancillary Agreements***" means the Pharmacovigilance Agreement, each Supply Agreement, and each Quality Agreement.

1.6 "***Applicable Law***" means applicable (with respect to the particular activity, task, or obligation under this Agreement to which such term applies) laws, statutes, rules, regulations, and other pronouncements having the effect of law of any Governmental Authority that may be in effect from time to time, including for clarity any applicable rules, regulations, guidelines, or other requirements of any Regulatory Authority that may be in effect from time to time.

1.7 "***Approved Labeling***" means, with respect to a Licensed Product and a jurisdiction: (a) the applicable Regulatory Authority-approved full prescribing information for such Licensed Product in such jurisdiction; and (b) the applicable Regulatory Authority-approved labels and any other written, printed, or graphic materials on any container, wrapper, or any package insert that is used with or for such Licensed Product in such jurisdiction.

1.8 "***ASMF***" has the meaning set forth in Section 5.3 (Correspondences with Regulatory Authorities).

1.9 "***Blocking Identified Rights***" has the meaning set forth in Section 2.7.2(a)ii (Acquisition of Potential In-Licenses).

1.10 "***Breach Notification***" has the meaning set forth in Section 14.2.1 (Material Breach).

1.11 "***Business Day***" means a day other than (a) a Saturday, Sunday, (b) a day on which banking institutions in California, Tokyo, Japan, or London, England are required by Applicable Law to remain closed or (c) the nine consecutive days beginning on December 24 and continuing through January 1, to the extent not already covered in clause (a) or clause (b).

1.12 "***Calendar Quarter***" means, with respect to the first Calendar Quarter during the Term, the period beginning on the Effective Date and ending on the last day of the Calendar Quarter within which the Effective Date falls, and thereafter each successive period of three calendar months ending on (and including) each of March 31, June 30, September 30, and December 31; except that the last Calendar Quarter during the Term will end upon the expiration of the Term.

1.13 "***Calendar Year***" means the period of 12 consecutive calendar months beginning on January 1 and ending on December 31; except that (a) the first Calendar Year during the Term will begin on the Effective Date and end on December 31 of the Calendar Year within which the Effective Date falls, and (b) the last Calendar Year during the Term will end upon expiration of the Term.

1.14 "***Change of Control***" means, with respect to a Party, that: (a) any Third Party acquires directly or indirectly the beneficial ownership of any voting security of such Party, or if the percentage ownership of such Third Party in the voting securities of such Party is increased through stock redemption, cancellation, or other recapitalization, and immediately after such acquisition or increase such Third Party is, directly or indirectly, the beneficial owner of voting securities representing more than 50% of the total voting power of all of the then outstanding voting securities of such Party; (b) a merger, consolidation, recapitalization, or reorganization of such Party is consummated that would result in shareholders or equity holders of such Party immediately prior to such transaction owning 50% or less of the outstanding voting securities of the surviving entity (or its parent entity) immediately following such transaction; or (c) the sale or transfer to a Third Party, in one or more related transactions, of all or substantially all of such Party's consolidated assets taken as a whole.

1.15 "***Clinical Supply Agreement***" has the meaning set forth in Section 7.2.1 (Clinical Supply Agreement).

1.16 "***Clinical Trial***" means any clinical trial in humans.

1.17 "***CMC***" means chemistry, manufacturing, and controls.

1.18 "***CMO***" has the meaning set forth in Section 7.3.1 (By Otsuka).

1.19 "***Collaboration In-License***" means (a) any Potential In-License that [***] in accordance with Section 2.7.2(b) (Collaboration In-Licenses) and (b) any Existing Third-Party IP Agreement.

1.20 "***Collaboration Know-How***" means all Know-How developed or invented by a Party's or its Affiliates', licensees', Sublicensees', or Subcontractors' employees, agents, or independent contractors, or any Persons contractually required to assign or license such Know-How to such Party or any Affiliate of such Party, either alone or jointly with the other Party's or its Affiliates', licensees', Sublicensees', or Subcontractors' employees, agents, or independent contractors, or any Persons contractually required to assign or license such Know-How to such other Party or any Affiliate of such other Party, in each case, in the performance of activities under this Agreement during the Term.

1.21 "***Collaboration Patent Rights***" means any Patent Right that (a) has a priority date after the Effective Date and (b) Covers any Invention included in the Collaboration Know-How.

1.22 "***Combination Product***" has the meaning set forth in Section 1.136 of this Appendix 1 (Definitions).

1.23 "***Combination Product Net Sales***" has the meaning set forth in Section 1.136 of this Appendix 1 (Definitions).

1.24 "***Commercial Supply Agreement***" has the meaning set forth in Section 7.2.2 (Commercial Supply Agreement).

1.25 "***Commercialization***" means any and all activities directed to the marketing, promotion, distribution, pricing, reimbursement, offering for sale, and sale of a pharmaceutical or biologic product and interacting with Regulatory Authorities following receipt of Regulatory Approval in the applicable country or region for such pharmaceutical or biologic product regarding the foregoing, including seeking and maintaining any required Reimbursement Approval, but excluding activities directed to Manufacturing or Development. "***Commercialize***," "***Commercializing***," and "***Commercialized***" will be construed accordingly.

1.26 "***Commercially Reasonable Efforts***" means, with respect to the Exploitation of a Licensed Product by a Party, [***].

1.27 "***Competitive Infringement***" means any infringement, unauthorized use, misappropriation or threatened infringement or misappropriation by a Third Party with respect to any Ionis Technology, Otsuka Technology, or Joint Collaboration Technology by reason of the making, using, offering to sell, selling or importing of a compound, product, method, or process that would be competitive with a Licensed Product then being Developed or Commercialized in the Field.

1.28 "***Confidential Disclosure Agreement***" has the meaning set forth in Section 16.2 (Entire Agreement; Amendment).

1.29 "***Confidential Information***" means, subject to Section 12.3 (Exemptions), (a) Know-How and any technical, scientific, trade, research, Manufacturing, business, financial, marketing, product, supplier, intellectual property, and other non-public or proprietary data or information (including unpublished patent applications) that may be disclosed by one Party (the "***Disclosing Party***") or its Affiliates to the other Party (the "***Receiving Party***") or its Affiliates pursuant to this Agreement (including information disclosed prior to the Effective Date pursuant to the Confidential Disclosure Agreement), regardless of whether such information is specifically marked or designated as confidential and regardless of whether such information is in written, oral, electronic, or other form, and (b) the terms of this Agreement.

1.30 "***Continuing Know-How Transfer***" has the meaning set forth in Section 3.1 (Initial Know-How Transfer).

1.31 **"*Control*" or "*Controlled*"** means the possession by a Party (whether by ownership, license, or otherwise other than pursuant to this Agreement) of, (a) with respect to any materials or other tangible Know-How, the legal authority or right to physical possession of such materials or tangible Know-How, with the right to provide such materials or tangible Know-How to the other Party on the terms set forth herein, (b) with respect to Patent Rights, Regulatory Approvals, Regulatory Submissions, intangible Know-How, or other intellectual property, the legal authority or right to grant a license, sublicense, access, or right to use (as applicable) to the other Party under such Patent Rights, Regulatory Approvals, Regulatory Submissions, intangible Know-How, or other intellectual property on the terms set forth herein, in each case ((a) and (b)), without breaching or otherwise violating the terms of any arrangement or agreement with a Third Party in existence as of the time such Party or its Affiliates would first be required hereunder to grant the other Party such access, right to use, licenses, or sublicense or incurring any additional payment obligations to a Third Party that would not be incurred but for such access, right to use, licenses, or sublicense, other than payment obligations incurred under a Collaboration In-License, and (c) with respect to any product, the possession by a Party of the ability (whether by sole or joint ownership, license, or otherwise, other than pursuant to the licenses granted under this Agreement) to grant an exclusive license or sublicense of Patent Rights that Cover such product or proprietary Know-How that is used in connection with the Exploitation of such product. Notwithstanding the foregoing, [***].

1.32 "***Core or Manufacturing Identified Rights***" has the meaning set forth in Section 2.7.2(a)i (Acquisition of Potential In-Licenses).

1.33 "***Core or Manufacturing Potential In-License***" has the meaning set forth in Section 2.7.2(a)i (Acquisition of Potential In-Licenses).

1.34 "***Cost Overrun***" has the meaning set forth in Section 4.4.2(b) (Cost Overruns).

1.35 "***Cover***" means, with respect to a particular subject matter at issue and a relevant Patent Right or individual claim in such Patent Right, as applicable, that the manufacture, use, sale, offer for sale, or importation of such subject matter would fall within the scope of one or more claims in such Patent Right.

1.36 "***Cross-Territory Clinical Development Plan***" has the meaning set forth in Section 4.2.1 (Cross-Territory Clinical Development Plan).

1.37 "***Cross-Territory Clinical Studies***" has the meaning set forth in Section 4.2.1 (Cross-Territory Clinical Development Plan).

1.38 "***Debarred/Excluded***" has the meaning set forth in Section 11.1.5 (Mutual Representations and Warranties).

1.39 "***Development***" means all internal and external research, development and regulatory activities regarding pharmaceutical or biologic products, including (a) research, process development, non-clinical testing, toxicology, non-clinical activities, IND-enabling studies, and Clinical Trials, and (b) preparation, submission, review, and development of data or information for the purpose of submission to a Regulatory Authority to obtain authorization to conduct Clinical Trials and to obtain, support, or maintain Regulatory Approval of a pharmaceutical or biologic product, but excluding activities directed to Manufacturing or Commercialization. Development will include development and regulatory activities for additional presentations or indications for a product after receipt of Regulatory Approval of such product, including Post-Approval Mandatory Studies. "***Develop***," "***Developing***," and "***Developed***" will be construed accordingly.

1.40 "***Development Cost Share Notice***" has the meaning set forth in Section 4.4.3 (Shared Cross-Territory Development Costs).

1.41 "***Disclosing Party***" has the meaning set forth in Section 1.29 (Confidential Information) of this Appendix 1 (Definitions).

1.42 "***Disputed Matter***" has the meaning set forth in Section 15.1 (Executive Officers: Disputes).

1.43 "***Effective Date***" has the meaning set forth in the Preamble.

1.44 "***Eligible Cross-Territory Development Costs***" has the meaning set forth in Section 4.4.3 (Shared Cross-Territory Development Costs).

1.45 "***EMA***" means the European Medicines Agency or any successor agency thereto.

1.46 "***European Union***" or "**E.U.**" means the economic, scientific, and political organization of member states of the European Union as it may be constituted from time to time.

1.47 "[***]" has the meaning set forth in Section 7.2.6 ([***]).

1.48 "***Executive Officer***" means (a) with respect to Otsuka, its President and Representative Director or their designee and (b) with respect to Ionis, the Chief Executive Officer or their designee.

1.49 "***Existing Third-Party IP Agreement***" means any agreement between Ionis (or any of its Affiliates) and any Third Party entered into prior to the Effective Date under which Ionis (or any of its Affiliates) obtained a license or other right to any of such Third Party's Know-How or Patent Rights that fall within the definition of any of the Ionis Technology.

1.50 "***Exploit***" means to make, have made, use, offer to sell, sell, Develop, Manufacture, Commercialize, or otherwise exploit. "***Exploitation***" will be construed accordingly.

1.51 "***External Costs***" mean, with respect to a Party, the documented actual expenses paid to Third Parties (or payable to Third Parties and accrued in accordance with such Party's Accounting Standards) by such Party (or its Affiliate) in consideration of the performance of activities under this Agreement, without mark-up, and excluding any costs or expenses included under the FTE Rate.

1.52 "***FD&C Act***" means the United States Federal Food, Drug and Cosmetic Act, as amended from time-to-time, together with any rules, regulations, and requirements promulgated thereunder (including all additions, supplements, extensions, and modifications thereto).

1.53 "***FDA***" means the U.S. Food and Drug Administration or any successor agency thereto.

1.54 "***Field***" means for the treatment or prevention of any diseases and conditions in humans.

1.55 "***Filing Party***" has the meaning set forth in Section 5.5 (Regulatory Submissions).

1.56 "***First Commercial Sale***" means, with respect to a Licensed Product in a country, the first sale for end use or consumption to a Third Party of such Licensed Product in such country by a Party, or its Affiliates or Sublicensees after the receipt of Regulatory Approval and Reimbursement Approval in the Field for such Licensed Product by the relevant Regulatory Authority in such country. First Commercial Sale excludes any sale or other distribution for use in a Clinical Trial or other Development activity or for compassionate use, named-patient use, or expanded access, indigent or other patient access programs when sold or distributed at or below the applicable Selling Party's costs.

1.57 "[***]" has the meaning set forth in Section 9.3.4(a) ([***]).

1.58 "***Follow-On Product***" has the meaning set forth in Section 2.8.1 (ROFN Exercise).

1.59 "***Follow-On Product Activities***" has the meaning set forth in Section 2.8.3 (Follow-On Product Activities).

1.60 "***Force Majeure***" has the meaning set forth in Section 16.5 (Force Majeure).

1.61 "***FTE***" means the equivalent of the work of one duly qualified employee of a Party full time for one year (consisting of a total of [***] hours per year) directly carrying out [***] activities under this Agreement. Overtime, and work on weekends, holidays and the like will not be counted with any multiplier (*e.g.*, time-and-a-half or double time) toward the number of hours that are used to calculate the FTE contribution, and no individual may be charged at greater than one FTE, regardless of that individual's hours worked during that year. The portion of an FTE billable by a Party for one employee during a given accounting period will be determined by dividing the number of hours worked directly by such employee on the work to be conducted under this Agreement during such accounting period by the number of FTE hours applicable for such accounting period based on [***] working hours per Calendar Year. For clarity, travel time spent by an employee, unless also spent working directly on activities under this Agreement, will not be included in the number of hours used to calculate the FTE contribution.

1.62 "***FTE Rate***" means [***] per FTE per hour. For the avoidance of doubt, such FTE Rate will be [***].

1.63 "***Future Cross-Territory Studies***" has the meaning set forth in Section 4.2.1 (Cross-Territory Clinical Development Plan).

1.64 "***GAAP***" means the generally accepted accounting principles in the United States.

1.65 "***Generic Product***" means, with respect to a Licensed Product in a country, a pharmaceutical product (other than such Licensed Product) that (a) is expected to be sold by a Third Party other than a Sublicensee under license from Otsuka in such country, (b) is authorized for use in such country in one or more of the indications for which such Licensed Product has Regulatory Approval in such country; and (c) contains the same active pharmaceutical ingredient(s) as such Licensed Product. A product will not be considered to be a Generic Product if (i) Otsuka or any of its Affiliates or Sublicensees was involved in or authorized the Development or Commercialization of such product, (ii) Otsuka or any of its Affiliates or Sublicensees has granted a license to such Third Party in respect of such product, or (iii) such product is Commercialized by any Person who obtained such product in a chain of distribution that included Otsuka or any of its Affiliates or Sublicensees.

1.66 "***Global Brand Strategic and Operating Plan***" has the meaning set forth in Section 6.4 (Global Brand Strategic and Operating Plan).

1.67 "***Global Medical Affairs Plan***" has the meaning set forth in Section 6.7.1 (Global Medical Affairs Plan).

1.68 "***Global Trade Control Laws***" means the U.S. Export Administration Regulations, the U.S. International Traffic in Arms Regulations, the economic sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Control, E.U. Council Regulations on export controls, including Nos. 428/2009, 267/2012, other E.U. Council sanctions regulations, as implemented in the E.U. member states, United Nations sanctions policies, and all relevant regulations made under any of the foregoing.

1.69 "***Good Clinical Practices***" or "***GCP***" means the then-current good clinical practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.70 "***Good Laboratory Practices***" or "***GLP***" means the then-current good laboratory practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.71 "***Good Manufacturing Practices***" or "***GMP***" means the then-current good manufacturing practice standards, practices, and procedures promulgated or endorsed by the applicable Regulatory Authority as set forth in the guidelines imposed by such Regulatory Authority, as may be updated from time-to-time.

1.72 "***Government Official***" means any official, officer, employee, or representative of: (a) any federal, state, provincial, administrative division, county, or municipal government or any department or agency thereof; (b) any public international organization or any department or agency thereof; or (c) any company or other entity owned or controlled by any government or Governmental Authority.

1.73 "***Governmental Authority***" means any court, agency, department, authority, tribunal, or other instrumentality of any supra-national, national, state, provincial, county, city, or other political subdivision. For clarity, Governmental Authorities include all Regulatory Authorities.

1.74 "***HAE***" means hereditary angioedema.

1.75 "***Identified Rights***" has the meaning set forth in Section 2.7.1 (Identification of New In-License Agreements).

1.76 "***IFRS***" means International Financial Reporting Standards, consistently applied.

1.77 "***IND***" means an Investigational New Drug application required pursuant to 21 C.F.R. Part 312 or any comparable filings outside of the U.S. required to commence human clinical trials in such country or region (such as an application for a Clinical Trial Authorization in the E.U.), and all supplements or amendments that may be filed with respect to the foregoing.

1.78 "***Indemnified Party***" has the meaning set forth in Section 13.3 (Indemnification Procedure).

1.79 "***Indemnifying Party***" has the meaning set forth in Section 13.3 (Indemnification Procedure).

1.80 "***Initial Know-How Transfer***" has the meaning set forth in Section 3.1 (Initial Know-How Transfer).

1.81 "***Initial Royalties***" has the meaning set forth in Section 9.3.1 (Royalty Payments During the Initial Royalty Term).

1.82 "***Initial Royalty Term***" has the meaning set forth in Section 9.3.1 (Royalty Payments During the Initial Royalty Term).

1.83 "***Initiation***" means dosing of the first patient in a Clinical Trial.

1.84 "***Internal Costs***" means, for any period of time, the product obtained by multiplying (a) the total FTEs (or portion thereof) devoted to the performance of activity under this Agreement during such period, by (b) the applicable FTE Rate for such period; *provided* that [***].

1.85 "***Invention***" means any process, method, composition of matter, article of manufacture, discovery, or finding that is conceived or reduced to practice (whether or not patentable).

1.86 "***Ionis Attribution Language***" has the meaning set forth in Section 12.7.2 (Acknowledgement).

1.87 "***Ionis Collaboration Know-How***" has the meaning set forth in Section 10.1.2(a) (Ownership of Arising Intellectual Property).

1.88 "***Ionis Collaboration Patent Rights***" has the meaning set forth in Section 10.1.2(a) (Ownership of Arising Intellectual Property).

1.89 "***Ionis Core Technology***" means Ionis Core Technology Know-How and the Ionis Core Technology Patents.

1.90 "***Ionis Core Technology Know-How***" means, subject to Section 4.4.4(b) ([***] by Ionis), all Know-How, including Ionis Collaboration Know-How but excluding Ionis Product-Specific Know-How, Ionis Manufacturing and Analytical Know-How and Ionis' interest in any Joint Collaboration Know-How, that (a) is Controlled by Ionis or its Affiliates as of the Effective Date or at any time during the Term, (b) is necessary or reasonably useful to Exploit a Licensed Product, and (c) relates generally to oligonucleotide.

1.91 "***Ionis Core Technology Patents***" means, subject to Section 4.4.4(b) ([***] by Ionis), any Patent Rights, including Ionis Collaboration Patent Rights but excluding Ionis Product-Specific Patents, Ionis Manufacturing and Analytical Patents and Ionis' interest in any Joint Collaboration Patent Rights, that (a) are Controlled by Ionis or its Affiliates as of the Effective Date or at any time during the Term, (b) are necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product and (c) Cover subject matter generally applicable to oligonucleotides. A list of the Ionis Core Technology Patents as of the Effective Date is set forth on SCHEDULE 1.91 (Ionis Core Technology Patents); *provided* that, any Patent Right existing as of the Effective Date that otherwise would be included in the definition of Ionis Core Technology Patents but is not included on SCHEDULE 1.91 (Ionis Core Technology Patents) will still be considered a Ionis Core Technology Patent.

1.92 "***Ionis Indemnitee***" has the meaning set forth in Section 13.2 (Indemnification by Otsuka).

1.93 "***Ionis Internal Oligonucleotide Safety Database***" has the meaning set forth in Section 5.12.1 (Ionis Internal Oligonucleotide Safety Database).

1.94 "***Ionis Know-How***" means the Ionis Core Technology Know-How, Ionis Manufacturing and Analytical Know-How, and Ionis Product-Specific Know-How.

1.95 "***Ionis Manufacturing and Analytical Know-How***" means, subject to Section 4.4.4(b) ([***] by Ionis), Know-How, including Ionis Collaboration Know-How but excluding Ionis' interest in any Joint Collaboration Know-How, that (a) is Controlled by Ionis or its Affiliates as of the Effective Date or at any time during the Term, (b) is necessary or reasonably useful to Exploit a Licensed Product, and (c) relates to any Manufacturing Technology.

1.96 "***Ionis Manufacturing and Analytical Patents***" means, subject to Section 4.4.4(b) ([***] by Ionis), Patent Rights, including Ionis Collaboration Patent Rights but excluding Ionis' interest in any Joint Collaboration Patent Rights, that (a) are Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Term, (b) are necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product, and (c) Cover Manufacturing Technology. A list of Ionis Manufacturing and Analytical Patents as of the Effective Date is set forth on Schedule 1.96 (Ionis Manufacturing and Analytical Patents); *provided* that, any Patent Right existing as of the Effective Date that otherwise would be included in the definition of Ionis Manufacturing and Analytical Patent but is not included on Schedule 1.96 (Ionis Manufacturing and Analytical Patents) will still be considered a Ionis Manufacturing and Analytical Patent.

1.97 "***Ionis Manufacturing and Analytical Technology***" means Ionis Manufacturing and Analytical Know-How and Ionis Manufacturing and Analytical Patents.

1.98 "***Ionis*** [***] ***Costs***" has the meaning set forth in Section 4.4.4(c) (Otsuka Opt-In).

1.99 "***Ionis*** [***]" has the meaning set forth in Section 4.4.4(b) ([***] by Ionis).

1.100 "***Ionis*** [***]" means [***] generated by or on behalf of Ionis in the [***] in accordance with Section 4.4.4(b) ([***] by Ionis).

1.101 "***Ionis Patent Rights***" means the Ionis Core Technology Patents, Ionis Manufacturing and Analytical Patents, and Ionis Product-Specific Patents.

1.102 "***Ionis Product-Specific Know-How***" means, subject to Section 4.4.4(b) ([***] by Ionis), all Know-How, including Ionis Collaboration Know-How but excluding Ionis' interest in any Joint Collaboration Know-How, that is (a) Controlled by Ionis or its Affiliates as of the Effective Date or at any time during the Term, (b) necessary or reasonably useful to Exploit a Licensed Product in the Field, and (c) specifically relating to (i) the composition of matter of a Licensed Product or (ii) methods of using a Licensed Product for the Field; *provided however*, Know-How that (i) consists of subject matter applicable to oligonucleotide compounds or products in general or (ii) relates to an oligonucleotide compound that does not specifically modulate expression of PKK via the binding, partially or wholly, of such compound to RNA that encodes PKK, will not be considered Ionis Product-Specific Know-How, and in each case of (i) and (ii), such Know-How will be considered Ionis Core Technology Know-How.

1.103 "***Ionis Product-Specific Patents***" means, subject to Section 4.4.4(b) ([***] by Ionis), all Product-Specific Patents, excluding Ionis' interest in any Joint Collaboration Patent Rights, that are (a) Controlled by Ionis or its Affiliates on the Effective Date or at any time during the Term and (b) necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product; *provided*, *however*, that Patent Rights that include only claims that are directed to (i) subject matter applicable to oligonucleotide compounds or products in general or (ii) an oligonucleotide compound that does not specifically modulate expression of PKK via the binding, partially or wholly, of such compound to RNA that encodes PKK, will not be considered Ionis Product-Specific Patents, and in each case of (i) and (ii), such Patent Rights will be considered Ionis Core Technology Patents. A list of Ionis Product-Specific Patents as of the Effective Date is set forth on Schedule 1.103 (Ionis Product-Specific Patents); *provided* that, any Patent Right existing as of the Effective Date that otherwise would be included in the definition of Ionis Product-Specific Patent but is not included on Schedule 1.103 (Ionis Product-Specific Patents) will still be considered a Ionis Product-Specific Patent.

1.104 "***Ionis Product-Specific Technology***" means Ionis Product-Specific Know-How and Ionis Product-Specific Patents.

1.105 "***Ionis Product Trademarks***" has the meaning set forth in Section 10.10.1(c) (Ownership of Ionis Product Trademarks).

1.106 "***Ionis Prosecuted Patent Rights***" has the meaning set forth in Section 10.2.1(a) (Right to Prosecute).

1.107 "***Ionis Publication***" has the meaning set forth in Section 12.5.2 (Ionis' Right to Publish).

1.108 "***Ionis Regulatory Activities***" has the meaning set forth in Section 5.1 (Regulatory Responsible Party).

1.109 "***Ionis Technology***" means the Ionis Know-How, the Ionis Patent Rights, and Ionis' interest in the Joint Collaboration Technology.

1.110 "***Ionis Territory***" means worldwide, except for the Otsuka Territory.

1.111 "***IRS***" has the meaning set forth in Section 9.10.3 (Tax Cooperation).

1.112 "***Joint Collaboration Know-How***" means all Collaboration Know-How that is developed or invented jointly by a Party's or its Affiliates', licensees', Sublicensees', or Subcontractors' employees, agents, or independent contractors, or any Persons contractually required to assign or license such Collaboration Know-How to such Party or any Affiliate of such Party, on the one hand, and the other Party's or its Affiliates', licensees', Sublicensees', or Subcontractors' employees, agents, or independent contractors, or any Persons contractually required to assign or license such Collaboration Know-How to such Party or any Affiliate of such Party, on the other hand.

1.113 "***Joint Collaboration Patent Rights***" means all Collaboration Patent Rights that Cover Joint Collaboration Know-How.

1.114 "***Joint Collaboration Technology***" means the Joint Collaboration Know-How and the Joint Collaboration Patent Rights.

1.115 "***JSC***" has the meaning set forth in Section 8.1.1 (Formation and Purpose of the JSC).

1.116 "***JSC Co-Chairperson***" has the meaning set forth in Section 8.1.2 (Membership).

1.117 "***Know-How***" means proprietary Inventions, discoveries, trade secrets, materials, information, experience, data, formulas, procedures, technology, and results (whether or not patentable), including practices, knowledge, know-how, experience and test data (including physical, chemical, biological, toxicological, pharmacological, clinical and veterinary data), dosage regimens, assays, diagnostics, product specifications, manufacturing techniques and costs, analytical and quality control data and marketing, pricing and distribution costs, and sales practices, methods, data, and descriptions.

1.118 "***Knowledge***" means the actual knowledge, without any inquiry or investigation, of (a) with respect to Ionis, its [***]; and (b) with respect to Otsuka, its [***].

1.119 "***Licensed Compound***" means the GaINAc-conjugated antisense oligonucleotide compound known as donidalorsen.

1.120 "***Licensed Product***" means any pharmaceutical product that contains, comprises, or incorporates the Licensed Compound, in all current and future formulations and in any dosage strengths, presentations, or package configuration, and for any mode of administration. For clarity, any combination product comprised of an autoinjector pre-filled with the Licensed Compound is considered a Licensed Product. All products containing or comprising the same Licensed Compound, regardless of the formulation, indication, line extension or otherwise, will be considered the same Licensed Product for all purposes of this Agreement.

1.121 "***Losses***" has the meaning set forth in Section 13.1 (Indemnification by Ionis).

1.122 "***MAA***" or "Marketing Authorization Application" means any (a) New Drug Application as defined in the FD&C Act, (b) a marketing authorization application filed with (i) the EMA under the centralized EMA filing procedure to gain approval to market a biopharmaceutical in the E.U., or (ii) a Regulatory Authority in any country in the E.U. if the centralized EMA filing procedure is not used to gain approval to market a biopharmaceutical in the E.U., or (c) substantially similar application or submission to those set forth in clause (a) or clause (b) filed with a Regulatory Authority in a country or group of countries to obtain Regulatory Approval to Commercialize a biopharmaceutical or diagnostic product in that country or in that group of countries, in each case ((a) through (c)), including any amendments thereto, and supplemental applications, but excluding Reimbursement Approval applications.

1.123 "***MAA Acceptance***" means, with respect to a Marketing Authorization Application filed for a Licensed Product, the receipt of written notice of acceptance by the EMA of such Marketing Authorization Application for filing under the centralized filing procedure.

1.124 "[***]" means, [***].

1.125 "***Manufacture***" means activities directed to manufacturing, processing, packaging, labeling, filling, finishing, assembly, quality assurance, quality control, testing, and release, shipping, or storage of any pharmaceutical or biologic product (or any components or process steps involving any product or any companion diagnostic), placebo, or comparator agent, as the case may be, including qualification, validation, and scale-up, pre-clinical, clinical, and commercial manufacture and analytic development, product characterization, and stability testing, but excluding activities directed to Development, or Commercialization. "***Manufacturing***" and "***Manufactured***" will be construed accordingly.

1.126 "***Manufacturing Costs***" means, with respect to a Licensed Product [***].

1.127 "***Manufacturing Handover Date***" has the meaning set forth in Section 7.1.2 (Otsuka Manufacturing).

1.128 "***Manufacturing Handover Notice***" has the meaning set forth in Section 7.1.2 (Otsuka Manufacturing).

1.129 "***Manufacturing Technology***" means any or all of (a) methods or materials used in the synthesis or analysis of an oligonucleotide or a Licensed Product regardless of sequence or chemical modification, (b) methods of manufacturing components of an oligonucleotide, and (c) methods or materials used in Manufacturing a Licensed Product.

1.130 "***Manufacturing Technology Transfer***" has the meaning set forth in Section 7.4 (Manufacturing Technology Transfer).

1.131 "***Manufacturing Technology Transfer Agreement***" has the meaning set forth in Section 7.4 (Manufacturing Technology Transfer).

1.132 "***Medical Affairs***" means activities conducted by a Party's medical affairs department (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, review and approval of materials consistent with a Party's or its Affiliate's internal SOPs and Applicable Law, interactions and engagements with patient advocacy groups and other key stakeholders, and other similar medical programs and communications.

1.133 "***Milestone Events***" means the Regulatory Milestone Events and the Sales Milestone Events.

1.134 "***Milestone Payments***" means the Regulatory Milestone Payments and the Sales Milestone Payments.

1.135 "***Necessary Global In-License***" has the meaning set forth in Section 2.7.2(a) (Acquisition of Potential In-Licenses).

1.136 "***Net Sales***" means, with respect to any Licensed Product, the amount invoiced by Otsuka or its Affiliates or Sublicensees (each a "***Selling Party***") for sales of such Licensed Product in arm's length transactions to Third Parties in all countries in the Otsuka Territory, less deduction (if not already deducted in the amount invoiced) of the following items with respect to sales of such Licensed Product:

(a) Normal and customary trade, quantity, or cash discounts to non-affiliated brokers, agents or customers to the extent actually allowed and taken, *provided* that such discounts are not applied disproportionately to the Licensed Products when compared to the other products of the Selling Party, as applicable;

(b) Actual amounts repaid or credited by reason of rejections, returns, defects, price adjustments, billing errors, or trial prescriptions, including amounts repaid, discounted or credited by reason of risk sharing schemes with respect to the Licensed Product with any Governmental Authority;

(c) To the extent separately stated on purchase orders, invoices, or other documents of sale, any taxes, tariffs, duties, excises or other governmental charges (including any value added tax, sales tax, consumption tax or similar tax, other than any taxes based on income) imposed or levied on the production, sale, transportation, delivery, or use, exportation or importation of the Licensed Products;

(d) Rebates, reimbursements, fees, clawbacks, discounts or chargeback payments paid, granted or credited to managed health care organizations, pharmacy benefit managers (or equivalent thereof), national, state/provincial, local, and other governments or Governmental Authorities, their agencies/purchasers/reimbursement providers (including those requested by any Governmental Authority any time after the actual sale of a Licensed Product), or to any Third Party payor, administrator, contractee or purchaser, including trade customers, including any fees levied by any Governmental Authority as a result of healthcare reform policies, and including those offered as a result of the clinical or real-world performance of the Licensed Product after it is marketed and sold;

(e) Outbound transportation costs prepaid or allowed and costs of insurance in transit, with the exclusion of storage and warehousing costs;

(f) Any invoiced amounts that are not collected, including bad debts; and

(g) Any other deductions that are consistent with the Selling Party's Accounting Standards and are not duplicative of the above deductions;

provided that the following deductions are not allowed in the calculation of Net Sales: (i) co-payment assistance; (ii) discounts offered to insurers to facilitate patient access to the product; (iii) program and data management fees paid to wholesalers/distributors; (iv) commissions paid to third-party logistics (3PL) providers; and (v) product samples shipped to indirect customers.

If a Selling Party makes any adjustments to such deductions after the associated Net Sales have been reported pursuant to this Agreement, then the adjustments will be reported and reconciled with the next report and payment of any royalties due.

Net Sales will not include (i) any payments among Selling Parties, unless such paying party is the end user of the relevant Licensed Product, (ii) any payments in consideration of supplies of the applicable Licensed Product for use in Clinical Trials, or (iii) payments for promotional samples, compassionate use, named-patient use, or expanded access, indigent or other patient access programs, in each case when sold or distributed at or below the applicable Selling Party's costs (including supply price paid).

If a Selling Party sells a Licensed Product in the Otsuka Territory as part of a therapy or product in combination with other pharmaceutical or biologic products, diagnostic products, ingredients, delivery devices or other components other than the Licensed Compound (each, an "***Other Product***") whether combined in a single formulation or package, formulated or packaged separately but sold under a single label approved by a Regulatory Authority, packaged together for sale or shipment as a single unit, or marketed or sold collectively as a single product, but, in all cases, sold together for a single price (a "***Combination Product***"), Net Sales of such Combination Product for the purposes of determining payments based on Net Sales hereunder will be calculated by multiplying actual Net Sales of such Combination Product as determined in the first paragraph of this Net Sales definition ("***Combination Product Net Sales***") by the fraction A/(A+B) where A is the average selling price of the Licensed Compound sold separately in such country during the applicable reporting period, and B is the sum of the average selling price(s) of the Other Product(s) in the Combination Product in such country during the same reporting period. If the Licensed Compound is sold separately in an applicable reporting period in a country in the Otsuka Territory, but the Other Product(s) are not sold separately in the same country in the same reporting period, then Net Sales of such Combination Product will be calculated by multiplying the Combination Product Net Sales by the fraction A/C where A is the average selling price of the Licensed Compound sold separately in such country during such reporting period, and C is the average selling price of the Combination Product in such country during such reporting period. If neither the Licensed Compound nor the Other Product(s) are sold separately in the same country in the same reporting period, then Net Sales of such Combination Product will be calculated by multiplying the Combination Product Net Sales by a fraction that reflects the value of the Licensed Compound relative to the value of the Other Product(s) in such Combination Product, which fraction shall be determined by Otsuka in its reasonable judgment, and reasonably acceptable to Ionis, and in such event, Otsuka shall provide Ionis with supporting documentation for such determination. Notwithstanding the foregoing, the Parties agree that the Licensed Product Manufactured and supplied by Ionis pursuant to the Supply Agreements in the form of an autoinjector pre-filled with Licensed Compound will not be subject to the terms of this paragraph, and such autoinjector will not be deemed an Other Product for purposes of calculating Net Sales.

1.137 "[***]" has the meaning set forth in Section 4.4.4(a) (Shared Costs).

1.138 "[***]" has the meaning set forth in Section 4.4.4(a) (Shared Costs).

1.139 "***Non-Clinical HAE Development Plan***" has the meaning set forth in Section 4.2.2 (Non-Clinical HAE Development Plan).

1.140 "***OFAC***" means the Office of Foreign Assets Control of the United States Department of the Treasury or any successor agency thereto.

1.141 "***Ongoing Cross-Territory Studies***" has the meaning set forth in Section 4.2.1 (Cross-Territory Clinical Development Plan).

1.142 "***Opt-In Fee***" has the meaning set forth in Section 4.4.4(c) (Otsuka Opt-In).

1.143 "***Opt-In Notice***" has the meaning set forth in Section 4.4.4(c) (Otsuka Opt-In).

1.144 "***Other Covered Party***" means any political party or party official, or any candidate for political office.

1.145 "***Other Global In-License***" has the meaning set forth in Section 2.7.2(c) (Non-Approved Potential In-Licenses).

1.146 "***Other Product***" has the meaning set forth in Section 1.136 of this Appendix 1 (Definitions).

1.147 "***Otsuka Collaboration Know-How***" has the meaning set forth in Section 10.1.2(b) (Ownership of Arising Intellectual Property).

1.148 "***Otsuka Collaboration Patent Rights***" has the meaning set forth in Section 10.1.2(b) (Ownership of Arising Intellectual Property).

1.149 "***Otsuka Indemnitee***" has the meaning set forth in Section 13.1 (Indemnification by Ionis).

1.150 "***Otsuka Know-How***" means all Collaboration Know-How (excluding Otsuka's interest in Joint Collaboration Know-How) that is (a) Controlled by Otsuka or any of its Affiliates during the Term and (b) necessary or reasonably useful to Exploit a Licensed Product.

1.151 "***Otsuka Patent Rights***" means all Collaboration Patent Rights (excluding Otsuka's interest in Joint Collaboration Patent Rights) that are (a) Controlled by Otsuka or any of its Affiliates during the Term and (b) necessary or reasonably useful (or, with respect to patent applications, would be necessary or reasonably useful if such patent applications were to issue as patents) to Exploit a Licensed Product.

1.152 "***Otsuka Product Trademarks***" has the meaning set forth in Section 10.10.1(b) (Ownership of Otsuka Product Trademarks).

1.153 "***Otsuka Publication***" has the meaning set forth in Section 12.5.1 (Otsuka's Right to Publish).

1.154 "***Otsuka Technology***" means Otsuka Know-How, Otsuka Patent Rights, and Otsuka's interest in the Joint Collaboration Technology.

1.155 "***Otsuka Territory***" means (a) all members of the European Union or the European Economic Area (EEA) as of the Effective Date, and (b) the following countries: Iceland, Liechtenstein, Norway, Switzerland, and the United Kingdom.

1.156 "***Otsuka Territory Brand Strategic and Operating Plan***" has the meaning set forth in Section 6.5 (Otsuka Territory Brand Strategic and Operating Plan).

1.157 "***Otsuka Territory Medical Affairs Plan***" has the meaning set forth in Section 6.7.2 (Otsuka Territory Medical Affairs Plan).

1.158 "***Otsuka Territory-Specific Development Plan***" has the meaning set forth in Section 4.3 (Otsuka Territory-Specific Development Plan).

1.159 "***Otsuka Territory Trademark Infringement***" has the meaning set forth in Section 10.10.4(a) (Unitary Product Trademark).

1.160 "***Packaging and Labeling***" means primary, secondary, or tertiary packaging and labeling of a Licensed Product (in its commercial packaging presentation) for sale or use in a country, including the Approved Labeling and insertion of materials such as patient inserts, patient medication guides, and professional inserts and any other written, printed, or graphic materials accompanying such Licensed Product and any brand security or anti-counterfeiting measures included in the packaging elements for such Licensed Product considered to be part of the finished packaged Licensed Product, and all testing and release thereof.

1.161 "***Party Vote***" has the meaning set forth in Section 8.4.1 (General Decision-Making Process).

1.162 "***Patent Challenge***" means, with respect to a Person, that such Person contests or assists a Third Party in contesting the scope, validity, or enforceability of a Patent Right or any foreign counterpart thereof anywhere in the world in any court, tribunal, arbitration proceeding, or other proceeding, including the U.S. Patent and Trademark Office and the U.S. International Trade Commission. A Patent Challenge includes: (a) filing an action under 28 U.S.C. §§ 2201-2202 seeking a declaration of invalidity or unenforceability of any such Patent Right; (b) filing, or joining in, a petition under 35 U.S.C. § 311 to institute *inter partes* review of any such Patent Right; (c) filing, or joining in, a petition under 35 U.S.C. § 321 to institute post-grant review of any such Patent Right or any portion thereof; (d) filing or commencing any opposition, nullity, or similar proceedings challenging the validity of any such Patent Right in the Territory; or (e) any foreign equivalent of clauses (a), (b), (c), or (d), including any proceeding in any country or patent office in any country or region in the Otsuka Territory.

1.163 "***Patent Prosecution***" means activities directed to (a) preparing, filing, and prosecuting applications (of all types) for any Patent Right, (b) maintaining any Patent Right, and (c) deciding whether to abandon or maintain any Patent Right.

1.164 "***Patent Rights***" means (a) all patents, patent applications, and utility models in any country or jurisdiction, including provisional applications, priority applications, and international applications, (b) all patent applications filed either from such patents or patent applications or from an application claiming priority from any of these, including divisionals, continuations, and continuations-in-part, (c) any and all patents that have issued or in the future issue from the foregoing patent applications, (d) any and all substitutions, renewals, registrations, confirmations, revalidations, reissues, and re-examinations of the foregoing patents or patent applications, and (e) extensions, restorations, supplemental protection certificates, and the like based on any of the foregoing patents or patent applications.

1.165 "***Payment Assignment***" has the meaning set forth in Section 16.1 (Assignment).

1.166 "***Payment Forms***" means one copy of each of the following documents which, at the time Ionis provides such documents to Otsuka, must be currently effective (un-expired), completed and signed: the United States Internal Revenue Service Form 6166 (United States Residency Certification) as received from the United States Internal Revenue Service; Form 3 (Application Form for Income Tax Convention); and Form 17 (Attachment Form for Limitation on Benefits Article).

1.167 "***Person***" means any corporation, limited or general partnership, limited liability company, joint venture, trust, unincorporated association, governmental body, authority, bureau, or agency, or any other entity or body, or an individual.

1.168 "***Pharmacovigilance Agreement***" means an agreement regarding receipt, investigation, and reporting of product complaints, adverse events, product recalls, and any other information related to the safety of the Licensed Products in the Territory.

1.169 "***Phase 3 Clinical Trial***" means a Clinical Trial of a Licensed Product that satisfies the requirements for a Phase 3 study as defined in 21 CFR § 312.21(c) (or any amended or successor regulations) or that satisfies the requirements of similar laws or regulations outside the United States.

1.170 "[***]" means the [***].

1.171 "***Post-Approval Cross-Territory Mandatory Studies***" has the meaning set forth in Section 4.2.1 (Cross-Territory Clinical Development Plan).

1.172 "***Post-Approval Mandatory Study***" means any Clinical Trial or other study of a pharmaceutical or biologic product initiated following receipt of Regulatory Approval or to be conducted after receipt of Regulatory Approval, in each case, that was mandated by the applicable Regulatory Authority in any country in the Territory as a condition of receiving or maintaining a Regulatory Approval for a product with respect to a particular indication in such country (such as post-marketing approval studies and observational studies, if required by any Regulatory Authority in any country in the Territory to support or maintain Regulatory Approval for a product in such country) or that is required for a label extension for a product in such country. For clarity, a [***] is a Post-Approval Mandatory Study.

1.173 "***Potential In-License***" has the meaning set forth in Section 2.7.2(a) (Acquisition of Potential In-Licenses).

1.174 "***Product Materials***" has the meaning set forth in Section 6.9 (Product Materials).

1.175 "***Product-Specific Patents***" means Patent Rights Controlled by a Party or any of its Affiliates as of or after the Effective Date claiming: (a) the composition of matter of a Licensed Product, or (b) methods of using a Licensed Product.

1.176 "***Professional Requirements***" means (a) the codes and standards of the European Accreditation Council for Continuing Medical Education (EACCME) and the European Federation of Pharmaceutical Industries and Associations (EFPIA), (b) the codes of the Prescription Medicines Code of Practice Authority (PMCPA) and the Association of the British Pharmaceutical Industry (ABPI), (c) FDA's regulations, guidance, and enforcement letters concerning the advertising of prescription drug products, (d) the American Medical Association's Guidelines on Gifts to Physicians from Industry, (e) the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support of Continuing Medical Education, (f) the Pharmaceutical Supply Chain Initiative (PSCI) and Pharmaceutical Industry Principles for Responsible Supply Chain Management, (g) the Code on Interactions with Healthcare Professionals promulgated by the Pharmaceutical Research and Manufacturers of America (PhRMA Code), (h) the Department of Health and Human Services Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers (OIG Compliance Guidance), and (i) all other accepted national and international pharmaceutical industry codes of practice in and for the relevant countries in the Territory, as any of the foregoing may be amended from time-to-time.

1.177 "***Publication***" has the meaning set forth in Section 12.5 (Publications).

1.178 "***PV Subcommittee***" has the meaning set forth in Section 5.11 (Pharmacovigilance Subcommittee).

1.179 "[***]" means [***].

1.180 "***Quality Agreement***" has the meaning set forth in Section 7.2.3 (Quality Agreements).

1.181 "***Receiving Party***" has the meaning set forth in Section 1.29 (Confidential Information) of this Appendix 1 (Definitions).

1.182 "***Reduced Royalties***" has the meaning set forth in Section 9.3.3 (Reduced Royalty Term).

1.183 "***Reduced Royalty Term***" has the meaning set forth in Section 9.3.3 (Reduced Royalty Term).

1.184 "[***]" has the meaning set forth in Section 9.3.2(c) ([***]).

1.185 "***Regulatory Approval***" means, with respect to a particular country or other regulatory jurisdiction, any approval of an MAA or other approval, product, or establishment license, registration, or authorization of any Regulatory Authority necessary for the commercial sale of a pharmaceutical, diagnostic, or biologic product in such country or other regulatory jurisdiction, excluding, in each case, Reimbursement Approval.

1.186 "***Regulatory Authority***" means, in a particular country or jurisdiction, any applicable Governmental Authority involved in granting Regulatory Approval in such country or jurisdiction, including (a) in the U.S., the FDA and any other applicable Governmental Authority in the U.S. having jurisdiction over any pharmaceutical, diagnostic, or biologic product, (b) in the E.U., the EMA and any other applicable Governmental Authority in the E.U. having jurisdiction over any pharmaceutical, diagnostic, or biologic product, and (c) in other countries, other analogous Governmental Authorities having jurisdiction over any pharmaceutical, diagnostic, or biologic product.

1.187 "***Regulatory Exclusivity***" means, with respect to a Licensed Product in a country in the Otsuka Territory, the period of time during which: (a) Otsuka or its Affiliate or Sublicensee has been granted the exclusive legal right by a Regulatory Authority (or is otherwise entitled to the exclusive legal right by operation of Applicable Law) in such country to market and sell such Licensed Product, and such right precludes a Third Party from making such Licensed Product available for purchase for any indication; or (b) the data and information submitted by Otsuka or its Affiliate or Sublicensee to the relevant Regulatory Authority in such country for purposes of obtaining Regulatory Approval of such Licensed Product may not be referenced, or relied upon in any way by a Third Party or such Regulatory Authority to support the Regulatory Approval or marketing of any product by a Third Party in such country, or if such data and information is referenced, or relied upon to support a Regulatory Approval granted to a Third Party in such country, the product may not be placed on the market for any indication.

1.188 "***Regulatory Milestone Events***" has the meaning set forth in Section 9.2.1 (Regulatory Milestones).

1.189 "***Regulatory Milestone Payments***" has the meaning set forth in Section 9.2.1 (Regulatory Milestones).

1.190 "***Regulatory Responsible Party***" means the Party designated under Section 5.1 (Regulatory Responsible Party).

1.191 "***Regulatory Subcommittee***" has the meaning set forth in Section 5.2 (Regulatory Subcommittee).

1.192 "***Regulatory Submission***" means any filing, application, or submission with any Regulatory Authority in support of the Development, Manufacture, Commercialization, or other Exploitation of a pharmaceutical, diagnostic, or biologic product (including to obtain, support, or maintain Regulatory Approval from that Regulatory Authority), and all written or electronic correspondence or communication with or from the relevant Regulatory Authority, as well as minutes of any material meetings, telephone conferences, or discussions with the relevant Regulatory Authority. Regulatory Submissions include all INDs, MAAs, and other applications for Regulatory Approval and their equivalents.

1.193 "***Regulatory Support***" has the meaning set forth in Section 5.6 (Cooperation).

1.194 "***Reimbursement Approval***" means, as applicable, (a) the Governmental Authority approval, agreement, determination, or other decision establishing prices that can be charged for a product in regulatory jurisdictions where the applicable Governmental Authority approves or determines the prices charged to end-users for pharmaceutical, diagnostic, or biologic products, or (b) the Governmental Authority approval, agreement, determination or decision establishing the prices at which a product will be reimbursed in regulatory jurisdictions where the applicable Governmental Authority approves, determines or recommends the reimbursement or use of pharmaceutical, diagnostic, or biologic products.

1.195 "***Remedial Action***" has the meaning set forth in Section 5.13.1 (Notification and Determination).

1.196 "***Representatives***" means, with respect to a Person, such Person's employees, officers, directors, consultants, contractors, Subcontractors and agents, in each case, who are authorized to act on behalf of such Person.

1.197 "***Requested Assistance***" has the meaning set forth in Section 3.2 (Technology Transfer Costs).

1.198 "***Restricted Party***" means any individual or entity on one or more of the Restricted Party Lists.

1.199 "***Restricted Party List***" means the list of sanctioned entities maintained by the United Nations; the Specially Designated Nationals and Blocked Persons List, the Foreign Sanctions Evaders List and the Sectoral Sanctions Identifications List, all administered by OFAC; the U.S. Denied Persons List, the U.S. Entity List, and the U.S. Unverified List, all administered by the U.S. Department of Commerce; and the entities subject to restrictive measures and the consolidated list of Persons, Groups, and Entities Subject to E.U. Financial Sanctions, as implemented by the E.U. Common Foreign & Security Policy.

1.200 "***Reversion License***" has the meaning set forth in Section 14.9.2(a) (License Grant).

1.201 "***Review Period***" has the meaning set forth in Section 12.5.1 (Otsuka's Right to Publish).

1.202 "***ROFN Exercise Notice***" has the meaning set forth in Section 2.8.1 (ROFN Exercise).

1.203 "***ROFN Negotiation Period***" has the meaning set forth in Section 2.8.2 (Negotiation).

1.204 "***ROFN Notice and Package***" has the meaning set forth in Section 2.8.1 (ROFN Exercise).

1.205 "***Royalties***" has the meaning set forth in Section 9.3.3 (Reduced Royalty Term).

1.206 "***Royalty Report***" has the meaning set forth in Section 9.3.4(b) (Royalty Report).

1.207 "***Royalty Term***" has the meaning set forth in Section 9.3.3 (Reduced Royalty Term).

1.208 "[***]" has the meaning set forth in Section 9.3.1 (Royalty Payments During the Initial Royalty Term).

1.209 "***Rules***" has the meaning set forth in Section 15.2.2 (Arbitration).

1.210 "***Sales Milestone Events***" has the meaning set forth in Section 9.2.2 (Sales Milestones).

1.211 "***Sales Milestone Payments***" has the meaning set forth in Section 9.2.2 (Sales Milestones).

1.212 "***Selling Party***" has the meaning set forth in Section 1.136 (Net Sales) of this Appendix 1 (Definitions).

1.213 "[***]" has the meaning set forth in Section 4.4.1(c) (Shared Development Costs).

1.214 "***Shared Cross-Territory Development Costs***" has the meaning set forth in Section 4.4.1(c) (Shared Development Costs).

1.215 "***Shared Development Budget***" has the meaning set forth in Section 4.4.2(a) (Shared Development Budget).

1.216 "***Subcommittee***" has the meaning set forth in Section 8.2.1 (Formation; Authority).

1.217 "***Subcommittee Co-Chairperson***" has the meaning set forth in Section 8.2.2 (Subcommittee Leadership and Meetings).

1.218 "***Subcontractors***" has the meaning set forth in Section 2.3.2 (Right to Subcontract).

1.219 "***Sublicensee***" means, with respect to a Party, any Third Party to which such Party or its Affiliate grants a sublicense under any of the rights licensed to the applicable Party under this Agreement other than a Subcontractor.

1.220 "***Supply Agreements***" has the meaning set forth in Section 7.2.2 (Commercial Supply Agreement).

1.221 "***Tax***" or "**Taxes**" means any present or future taxes, levies, imposts, duties, charges, assessments or fees of any nature (including any interest thereon), including value add, sales, excise or similar taxes.

1.222 "***Technology Transfer***" has the meaning set forth in Section 3.1 (Initial Know-How Transfer).

1.223 "***Term***" has the meaning set forth in Section 14.1 (Term).

1.224 "***Territory***" means (a) the Otsuka Territory, with respect to Otsuka, (b) the Ionis Territory, with respect to Ionis, and (c) collectively, worldwide.

1.225 "***Third Party***" means any Person other than a Party or its Affiliates.

1.226 "***Third Party Claims***" has the meaning set forth in Section 13.1 (Indemnification by Ionis).

1.227 "[***]" has the meaning set forth in Section 2.8.2 (Negotiation).

1.228 "***Third Party Patent Challenge***" has the meaning set forth in Section 10.4 (Defense of Third Party Patent Challenges).

1.229 "***Third Party Payments***" means, with respect to a Licensed Product, any (a) payments (including upfront payments, milestone payments, license fees, royalties and monetary damages) made by Otsuka or its Affiliate to a Third Party (i) pursuant to an agreement between Otsuka or its Affiliate and such Third Party entered into following the Effective Date in accordance with Section 2.7.2 (Potential In-Licenses) to obtain rights to Patent Rights or Know-How from such Third Party that would be infringed or misappropriated by the Exploitation of a Licensed Product in the Otsuka Territory or (ii) pursuant to an agreement between Otsuka or its Affiliate and such Third Party, or otherwise, as part of a settlement or to satisfy a judgment in accordance with Section 10.5.3 (Settlement), or (b) amounts for which Otsuka reimburses Ionis under a Collaboration In-License, in each case ((a) or (b)), that are directly in consideration for or reasonably allocable to a license or sublicense (as applicable) to Otsuka or its Affiliate under, or are paid in settlement or to satisfy a judgment of a claim relating to, Patent Rights or Know-How Controlled by such Third Party that would, but for a license thereunder, be infringed or misappropriated by the Exploitation of such Licensed Product.

1.230 "***Trademark***" means any word, name, symbol, color, shape, designation or any combination thereof, including any trademark, service mark, trade name, brand name, sub-brand name, domain name, trade dress, product configuration, program name, delivery form name, certification mark, collective mark, logo, tagline, slogan, design or business symbol, that functions as an identifier of source or origin, whether or not registered and all statutory and common law rights therein and all registrations and applications therefor, together with all goodwill associated with, or symbolized by, any of the foregoing.

1.231 "***Trademark Infringement Suit***" has the meaning set forth in Section 10.10.5(a) (Unitary Product Trademark).

1.232 "***Transition Plan***" has the meaning set forth in Section 14.9.3(a) (Scope).

1.233 "***Transition Services***" has the meaning set forth in Section 14.9.3(a) (Scope).

1.234 "***Unitary Product Trademark***" has the meaning set forth in Section 10.10.1(a) (Unitary Product Trademark).

1.235 "***Upfront Payment***" has the meaning set forth in Section 9.1 (Upfront Payment).

1.236 "***U.S.***" means the United States of America (including all possessions and territories thereof, including Puerto Rico).

1.237 "***U.S. Dollars***" or "**$**" means the legal tender of the U.S.

1.238 "***Valid Claim***" means a claim of an issued and unexpired patent (as may be adjusted through a patent term adjustment or extended through supplementary protection certificate or patent term extension or the like) that has not been revoked, held invalid, or held unenforceable by a patent office or other Governmental Authority of competent jurisdiction in a final and non-appealable judgment (or judgment from which no appeal was taken within the allowable time period), and [***].

1.239 "***Withheld Amount***" has the meaning set forth in Section 9.10.2 (Withholding Tax).

SCHEDULE 1.49

Existing Third-Party IP Agreements

[***]

SCHEDULE 1.91

Ionis Core Technology Patents

Ionis File No.	Country/Treaty	Application No./ Patent No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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<u>SCHEDULE 1.96</u>

Ionis Manufacturing and Analytical Patents

Ionis File No.	Country	Application No./ Patent No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]
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Schedule 1.103

Ionis Product-Specific Patents

Ionis File No.	Country/ Treaty	Status	Application No./ Patent No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]	[***]
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Ionis File No.	Country/ Treaty	Status	Application No./ Patent No.	Filing Date	Grant Date	Title
[***]	[***]	[***]	[***]	[***]	[***]	[***]
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Ionis File No.	Country/ Treaty	Status	Application No./ Patent No.	Filing Date	Grant Date	Title
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Ionis File No.	Country/ Treaty	Status	Application No./ Patent No.	Filing Date	Grant Date	Title
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SCHEDULE 4.2.1

Cross-Territory Clinical Development Plan

[***]

SCHEDULE 4.2.2

Non-Clinical HAE Development Plan

[***]

SCHEDULE 4.4.2

Shared Development Budget

[***]

SCHEDULE 14.9.3

Transition Services

[***]

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Akcea Therapeutics, Inc., a Delaware Corporation

Akcea Therapeutics Canada Inc., a Canadian Corporation

Akcea Therapeutics Germany GmbH, a German Corporation

Akcea Therapeutics UK Limited, a United Kingdom Limited Private Company

Akcea Therapeutics Ireland Limited, an Irish Private Company

Akcea Therapeutics Italia S.r.l., an Italian Company

Akcea Therapeutics Portugal, Unipessoal Lda, a Portuguese Company

Ionis Faraday LLC, a Delaware Corporation

Ionis Gazelle LLC, a Delaware Corporation

Ionis Ireland Limited, an Irish Private Company

Ionis USA Limited, a United Kingdom Limited Private Company

Osprey Therapeutics, Inc., a Delaware Corporation

Ionis Development (Ireland) Limited, an Irish Private Company

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements on Form S-3 (Nos. 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380, 333-141447, 333-151076, 333-188407, 333-217422, 333-242382, and 333-275741) 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, 333-258503, and 333-273902) of Ionis Pharmaceuticals, Inc. of our reports dated February 21, 2024, 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, 2023.

/s/ ERNST & YOUNG LLP

San Diego, California
February 21, 2024

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 21, 2024

/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 21, 2024

/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, 2023, 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 21, 2024

/s/ BRETT P. MONIA	/s/ ELIZABETH L. HOUGEN
Brett P. Monia, Ph.D.	Elizabeth L. Hougen
Chief Executive Officer	*Chief Financial Officer*

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

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

IONIS PHARMACEUTICALS, INC.

AMENDED AND RESTATED CLAWBACK POLICY

1. INTRODUCTION

The Board of Directors (the "***Board***") of Ionis Pharmaceuticals, Inc., a Delaware corporation (the "***Company***"), has determined that it is in the best interests of the Company and its stockholders to adopt this Amended and Restated Clawback Policy (this "***Policy***") providing for the Company's recoupment of Recoverable Incentive Compensation that is received by Covered Officers of the Company under certain circumstances. Certain capitalized terms used in this Policy have the meanings given to such terms in Section 3 below.

This Policy is designed to comply with, and shall be interpreted to be consistent with, Section 10D of the Exchange Act, Rule 10D-1 promulgated thereunder ("***Rule 10D-1***") and Nasdaq Listing Rule 5608 (the "***Listing Standards***"). This Policy amends and restates in its entirety that certain Clawback Policy, made effective March 23, 2021, previously adopted by the Board.

2. EFFECTIVE DATE

This Policy shall apply to all Incentive Compensation that is received by a Covered Officer on or after October 2, 2023 (the "***Effective Date***"). Incentive Compensation is deemed "***received***" in the Company's fiscal period in which the Financial Reporting Measure specified in the Incentive Compensation award is attained, even if the payment or grant of such Incentive Compensation occurs after the end of that period.

3. DEFINITIONS

"***Accounting Restatement***" means an accounting restatement that the Company is required to prepare due to the material noncompliance of the Company with any financial reporting requirement under the securities laws, including any required accounting restatement to correct an error in previously issued financial statements that is material to the previously issued financial statements, or that would result in a material misstatement if the error were corrected in the current period or left uncorrected in the current period.

"***Accounting Restatement Date***" means the earlier to occur of (a) the date that the Board, a committee of the Board authorized to take such action, or the officer or officers of the Company authorized to take such action if Board action is not required, concludes, or reasonably should have concluded, that the Company is required to prepare an Accounting Restatement, or (b) the date that a court, regulator or other legally authorized body directs the Company to prepare an Accounting Restatement.

"***Administrator***" means the Nominating, Governance and Review Committee of the Board or, in the absence of such committee, the Board. The Nominating, Governance and Review Committee of the Board will confer with the Compensation Committee of the Board on matters related to enforcement of this Policy.

"***Code***" means the U.S. Internal Revenue Code of 1986, as amended, and the regulations promulgated thereunder.

"***Compensation Committee***" means the Compensation Committee of the Board.

"***Covered Officer***" means each current and former Executive Officer.

"***Exchange***" means The Nasdaq Stock Market LLC.

"***Exchange Act***" means the U.S. Securities Exchange Act of 1934, as amended.

"***Executive Officer***" means each individual who is currently or was previously designated as an "officer" of the Company as defined in Rule 16a-1(f) of the Exchange Act.

"***Financial Reporting Measures***" means measures that are determined and presented in accordance with the accounting principles used in preparing the Company's financial statements, and any measures derived wholly or in part from such measures, including Company stock price and total stockholder return ("***TSR***"). A measure need not be presented in the Company's financial statements or included in a filing with the SEC in order to be a Financial Reporting Measure.

"***Incentive Compensation***" means any compensation that is granted, earned or vested based wholly or in part upon the attainment of a Financial Reporting Measure.

"***Lookback Period***" means the three completed fiscal years immediately preceding the Accounting Restatement Date, as well as any transition period (resulting from a change in the Company's fiscal year) within or immediately following those three completed fiscal years (except that a transition period of at least nine months shall count as a completed fiscal year). Notwithstanding the foregoing, the Lookback Period shall not include fiscal years completed prior to the Effective Date.

"***Recoverable Incentive Compensation***" means Incentive Compensation received by a Covered Officer during the Lookback Period that exceeds the amount of Incentive Compensation that would have been received had such amount been determined based on the Accounting Restatement, computed without regard to any taxes paid (*i.e.*, on a gross basis without regarding to tax withholdings and other deductions). For any compensation plans or programs that take into account Incentive Compensation, the amount of Recoverable Incentive Compensation for purposes of this Policy shall include, without limitation, the amount contributed to any notional account based on Recoverable Incentive Compensation and any earnings to date on that notional amount. For any Incentive Compensation that is based on stock price or TSR, where the Recoverable Incentive Compensation is not subject to mathematical recalculation directly from the information in an Accounting Restatement, the Administrator will determine the amount of Recoverable Incentive Compensation based on a reasonable estimate of the effect of the Accounting Restatement on the stock price or TSR upon which the Incentive Compensation was received. The Company shall maintain documentation of the determination of that reasonable estimate and provide such documentation to the Exchange in accordance with the Listing Standards.

"***SEC***" means the U.S. Securities and Exchange Commission.

4. RECOUPMENT

(a) Applicability of Policy. This Policy applies to Incentive Compensation received by a Covered Officer (i) after beginning services as an Executive Officer, (ii) who served as an Executive Officer at any time during the performance period for such Incentive Compensation, (iii) while the Company had a class of securities listed on a national securities exchange or a national securities association, and (iv) during the Lookback Period.

(b) Recoupment Generally. Pursuant to the provisions of this Policy, if there is an Accounting Restatement, the Company must reasonably promptly recoup the full amount of the Recoverable Incentive Compensation, unless the conditions of one or more subsections of Section 4(c) of this Policy are met and the Compensation Committee, or, if such committee does not consist solely of independent directors, a majority of the independent directors serving on the Board, has made a determination that recoupment would be impracticable. Recoupment is required regardless of whether the Covered Officer engaged in any misconduct and regardless of fault, and the Company's obligation to recoup Recoverable Incentive Compensation is not dependent on whether or when any restated financial statements are filed.

(c) Impracticability of Recovery. Recoupment may be determined to be impracticable if, and only if:

(i) the direct expense paid to a third party to assist in enforcing this Policy would exceed the amount of the applicable Recoverable Incentive Compensation; provided that, before concluding that it would be impracticable to recover any amount of Recoverable Incentive Compensation based on expense of enforcement, the Company shall make a reasonable attempt to recover such Recoverable Incentive Compensation, document such reasonable attempt(s) to recover, and provide that documentation to the Exchange in accordance with the Listing Standards; or

(ii) recoupment of the applicable Recoverable Incentive Compensation would likely cause an otherwise tax-qualified retirement plan, under which benefits are broadly available to employees of the Company, to fail to meet the requirements of Code Section 401(a)(13) or Code Section 411(a) and regulations thereunder.

(d) Sources of Recoupment. To the extent permitted by applicable law, the Administrator shall, in its sole discretion, determine the timing and method for recouping Recoverable Incentive Compensation hereunder, provided that such recoupment is undertaken reasonably promptly. The Administrator may, in its discretion, seek recoupment from a Covered Officer from any of the following sources or a combination thereof, whether the applicable compensation was approved, awarded, granted, payable or paid to the Covered Officer prior to, on or after the Effective Date: (i) direct repayment of Recoverable Incentive Compensation previously paid to the Covered Officer; (ii) cancelling prior cash or equity-based awards (whether vested or unvested and whether paid or unpaid); (iii) cancelling or offsetting against any planned future cash or equity-based awards; (iv) forfeiture of deferred compensation, subject to compliance with Code Section 409A; and (v) any other method authorized by applicable law or contract. Subject to compliance with any applicable law, the Administrator may effectuate recoupment under this Policy from any amount otherwise payable to the Covered Officer, including amounts payable to such individual under any otherwise applicable Company plan or program, *e.g.*, base salary, bonuses or commissions and compensation previously deferred by the Covered Officer. The Administrator need not utilize the same method of recovery for all Covered Officers or with respect to all types of Recoverable Incentive Compensation.

(e) No Indemnification of Covered Officers. Notwithstanding any indemnification agreement, applicable insurance policy or any other agreement or provision of the Company's certificate of incorporation or bylaws to the contrary, no Covered Officer shall be entitled to indemnification or advancement of expenses in connection with any enforcement of this Policy by the Company, including paying or reimbursing such Covered Officer for insurance premiums to cover potential obligations to the Company under this Policy.

(f) Indemnification of Administrator. Any members of the Administrator, and any other members of the Board who assist in the administration of this Policy, shall not be personally liable for any action, determination or interpretation made with respect to this Policy and shall be indemnified by the Company to the fullest extent under applicable law and Company policy with respect to any such action, determination or interpretation. The foregoing sentence shall not limit any other rights to indemnification of the members of the Board under applicable law or Company policy.

5. Administration

Except as specifically set forth herein, this Policy shall be administered by the Administrator. The Administrator shall have full and final authority to make any and all determinations required under this Policy. Any determination by the Administrator with respect to this Policy shall be final, conclusive and binding on all interested parties and need not be uniform with respect to each individual covered by this Policy. In carrying out the administration of this Policy, the Administrator is authorized and directed to consult with the full Board or such other committees of the Board as may be necessary or appropriate as to matters within the scope of such other committee's responsibility and authority. Subject to applicable law, the Administrator may authorize and empower any officer or employee of the Company to take any and all actions that the Administrator, in its sole discretion, deems necessary or appropriate to carry out the purpose and intent of this Policy (other than with respect to any recovery under this Policy involving such officer or employee).

6. Severability

If any provision of this Policy or the application of any such provision to a Covered Officer shall be adjudicated to be invalid, illegal or unenforceable in any respect, such invalidity, illegality or unenforceability shall not affect any other provisions of this Policy, and the invalid, illegal or unenforceable provisions shall be deemed amended to the minimum extent necessary to render any such provision or application enforceable.

7. No Impairment of Other Remedies

Nothing contained in this Policy, and no recoupment or recovery as contemplated herein, shall limit any claims, damages or other legal remedies the Company or any of its affiliates may have against a Covered Officer arising out of or resulting from any actions or omissions by the Covered Officer. This Policy does not preclude the Company from taking any other action to enforce a Covered Officer's obligations to the Company, including, without limitation, termination of employment and/or institution of civil proceedings. This Policy is in addition to the requirements of Section 304 of the Sarbanes-Oxley Act of 2002 that are applicable to the Company's Chief Executive Officer and Chief Financial Officer and to any other compensation recoupment policy and/or similar provisions in any employment, equity plan, equity award, or other individual agreement, to which the Company is a party or which the Company has adopted or may adopt and maintain from time to time.

8. Amendment; Termination

The Administrator may amend, terminate or replace this Policy or any portion of this Policy at any time and from time to time in its sole discretion. The Administrator shall amend this Policy as it deems necessary to comply with applicable law or any Listing Standard.

9. Successors

This Policy shall be binding and enforceable against all Covered Officers and, to the extent required by Rule 10D-1 and/or the applicable Listing Standards, their beneficiaries, heirs, executors, administrators or other legal representatives.

10. Required Filings

The Company shall make any disclosures and filings with respect to this Policy that are required by law, including as required by the SEC.

Ionis Pharmaceuticals, Inc.

Amended and Restated Clawback Policy

Form of Executive Acknowledgment

I, the undersigned, agree and acknowledge that I am bound by, and subject to, the Ionis Pharmaceuticals, Inc. Amended and Restated Clawback Policy, as may be amended, restated, supplemented or otherwise modified from time to time (the "***Policy***"). In the event of any inconsistency between the Policy and the terms of any employment agreement, offer letter or other individual agreement with Ionis Pharmaceuticals, Inc. (the "***Company***") to which I am a party, or the terms of any compensation plan, program or agreement, whether or not written, under which any compensation has been granted, awarded, earned or paid to me, the terms of the Policy shall govern.

In the event that the Administrator (as defined in the Policy) determines that any compensation granted, awarded, earned or paid to me must be forfeited or reimbursed to the Company pursuant to the Policy, I will promptly take any action necessary to effectuate such forfeiture and/or reimbursement. I further agree and acknowledge that I am not entitled to indemnification, and hereby waive any right to advancement of expenses, in connection with any enforcement of the Policy by the Company.

Agreed and Acknowledged:

Name: _____

Title: _____

Date: _____