IONIS®
A Genetic Medicines Company

Every Moment Matters

2022 | ANNUAL REPORT

FORWARD-LOOKING STATEMENTS

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

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

Summary of Risk Factors

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

- 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 the COVID-19 pandemic.

TRADEMARKS

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

CORPORATE INFORMATION

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

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

IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2022
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PART I

Item 1. Business

Overview

We were founded over 30 years ago to deliver innovative medicines for diseases with great medical need. Today, we are building on our advancements in RNA-targeted therapeutics to move us closer to achieving our vision to be the leader in genetic medicines. We believe our medicines have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases.

We currently have three marketed medicines: SPINRAZA, TEGSEDI and WAYLIVRA. Additionally, we have two medicines that will add to our commercial portfolio this year, assuming positive regulatory outcomes. These medicines are eplontersen to treat patients with polyneuropathy caused by hereditary transthyretin amyloidosis, or ATTRv-PN, and tofersen to treat patients with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS. We submitted the eplontersen New Drug Application, or NDA, to the U.S. Food and Drug Administration, or FDA, in December 2022. Tofersen is currently under regulatory review in the United States, or U.S., and European Union, or EU. In the U.S., tofersen has a Prescription Drug User Fee Act, or PDUFA, date of April 25, 2023. We also have a rich innovative late- and mid-stage pipeline primarily focused on our leading cardiovascular and neurology franchises. We currently have seven medicines in Phase 3 development. Additionally, based on recent positive data from the Phase 2 study of IONIS-FB-L_{Rx} in patients with immunoglobulin A nephropathy, or IgAN, Roche plans to advance IONIS-FB-L_{Rx} into Phase 3 development, which would further expand our late-stage pipeline.

Over the past year, we made important progress advancing our strategic priorities: to deliver an abundance of new medicines to the market, establish an integrated commercial organization and expand and diversify our technology platform. Last year, we delivered nine positive data readouts from our mid- and late-stage pipeline, positioning us to add to our commercial portfolio and our late-stage pipeline. We advanced our go-to-market plans for our near-term commercial opportunities, eplontersen, olezarsen and donidalorsen. We also expanded and diversified our technology when we advanced new medicines targeting muscle and using our MsPA backbone into preclinical development. Additionally, in late 2022, we entered into a collaboration with Metagenomi to add next generation gene editing capabilities to our technologies.

We accomplished all of this while earning revenues of $587 million for 2022 and ending the year with a cash and short-term investment balance of $2.0 billion. We strengthened our balance sheet with our recent sale and leaseback and royalty monetization transactions in late 2022 and January 2023, respectively. Under the sale and leaseback transaction, we received net proceeds of approximately $200 million, with the potential to receive additional payments of up to $40 million plus funding to expand our research and development, or R&D campus. Under our agreement with Royalty Pharma Investments, or Royalty Pharma, we received an upfront payment of $500 million in January 2023 when Royalty Pharma acquired a minority interest in our future SPINRAZA and pelacarsen royalties. Additionally, we have the potential to earn up to $625 million in pelacarsen milestone payments from Royalty Pharma.

Our multiple sources of revenue and strong balance sheet enable us to continue investing in our commercial readiness efforts for multiple late-stage programs and our innovative pipeline. By continuing to focus on these priorities, we believe we are well positioned to drive future growth and to deliver increasing value for patients and shareholders.

Marketed Medicines

SPINRAZA is the global market leader for the treatment of patients with spinal muscular atrophy, or SMA, a progressive, debilitating and often fatal genetic disease. Biogen is our partner responsible for commercializing SPINRAZA worldwide. From inception through December 31, 2022, we have earned more than $1.8 billion in revenues from our SPINRAZA collaboration, including more than $1.4 billion in royalties on sales of SPINRAZA.

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with ATTRv-PN. We launched TEGSEDI in the U.S. and the EU, in late 2018. In 2021, we began selling TEGSEDI in Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or Sobi, and in the second quarter of 2021, Sobi began distributing TEGSEDI in the U.S. and Canada. In Latin America, PTC Therapeutics International Limited, or PTC, is commercializing TEGSEDI in Brazil and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine that received conditional marketing authorization in May 2019 from the European Commission, or EC, as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA in Europe through our distribution agreement with Sobi. 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 Phase 3 Studies and Registration

We currently have seven medicines in Phase 3 studies for nine indications, which are:

- Eplontersen: our medicine in development for transthyretin amyloidosis, or ATTR
    - We are currently conducting the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN, the Phase 3 CARDIO-TTRansform study in patients with ATTR cardiomyopathy, or ATTR-CM, and additional studies supporting our ATTR development program
        - In December 2022, we submitted the NDA for eplontersen in the U.S. for patients with ATTRv-PN based on the positive results from an interim analysis of the Phase 3 NEURO-TTRansform study of eplontersen in patients with ATTRv-PN we first reported in June 2022
- Olezarsen: our medicine in development for FCS and severe hypertriglyceridemia, or SHTG
    - We are currently conducting a broad Phase 3 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 July 2022, we achieved full enrollment in the BALANCE Phase 3 study in patients with FCS with data expected in the second half of 2023
        - In the second half of 2022, we expanded our Phase 3 program for SHTG when we initiated CORE2, a confirmatory Phase 3 study of olezarsen in patients with SHTG and ESSENCE, a supporting Phase 3 study of olezarsen in patients with SHTG or hypertriglyceridemia and atherosclerotic cardiovascular disease
        - The FDA granted olezarsen fast track designation for the treatment of patients with FCS
- Donidalorsen: our medicine in development for hereditary angioedema, or HAE
    - We are currently conducting the Phase 3 OASIS-HAE study in patients with HAE and the Phase 3 OASIS-Plus supportive study for HAE patients previously treated with other prophylactic therapies
        - We reported positive data from the Phase 2 study and Phase 2 open-label extension, or OLE, study throughout 2022 and early 2023
- ION363: 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 ION363 in juvenile and adult patients with FUS-ALS
- Tofersen: our medicine in development for SOD1-ALS
    - Biogen is developing tofersen, including conducting the ongoing Phase 3 VALOR OLE study in patients with SOD1-ALS and the ongoing Phase 3 ATLAS study in presymptomatic SOD1 patients
        - Tofersen is currently under regulatory review in the U.S. with a PDUFA date of April 25, 2023 and in the EU
        - In June 2022, Biogen presented new positive data from the ongoing VALOR OLE study at the European Network to Cure ALS, or ENCALS, meeting. These data were included in the NDA filing and Marketing Authorization Application, or MAA, filing

- Pelacarsen: our medicine in development to treat patients with elevated lipoprotein(a), or Lp(a) and cardiovascular disease
    - Novartis is developing pelacarsen, including conducting the ongoing Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with established cardiovascular disease and elevated Lp(a)
        - In July 2022, Novartis achieved full enrollment in the Lp(a) HORIZON study
- Bepirovirsen: 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
        - In 2022, GSK presented positive data from the Phase 2b B-Clear study of bepirovirsen demonstrating potential for functional cures in patients with chronic HBV

COVID-19

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

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

SPINRAZA – SPINRAZA (nusinersen) injection for intrathecal use is a survival motor neuron-2, or SMN2, directed antisense medicine indicated for the treatment of spinal muscular atrophy, or 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, the *SMN2* gene can only produce approximately 10 percent of the SMN protein critical for motor neurons, resulting in severe and progressive loss of motor function and strength.

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

Biogen continues to expand the body of evidence supporting SPINRAZA's durable efficacy and well-established safety profile to address the remaining needs of SMA patients of all ages. 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, 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 2022, Biogen reported that increasing enrollment in the RESPOND study indicates there are residual unmet clinical needs in infants and toddlers with SMA who have unmet needs following gene therapy treatment.
- 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 of risdiplam. The first patient was treated in the ASCEND study in the first quarter of 2022.

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 open-label extension, or OLE, study for patients with SMA who participated in prior SPINRAZA studies.

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.

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.

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. 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.

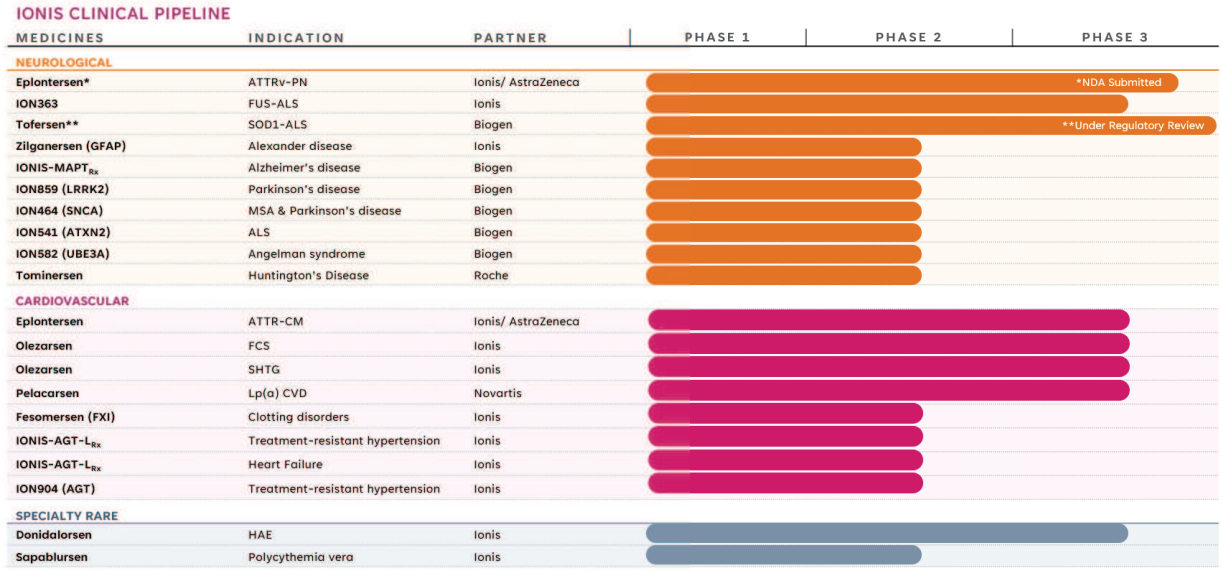
WAYLIVRA received conditional marketing authorization in May 2019 from the European Commission, or EC. WAYLIVRA is commercially available in multiple European countries and in Latin America. We launched WAYLIVRA in the EU in the third quarter of 2019. In 2021, we began selling WAYLIVRA in Europe through 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 Genetic Medicines

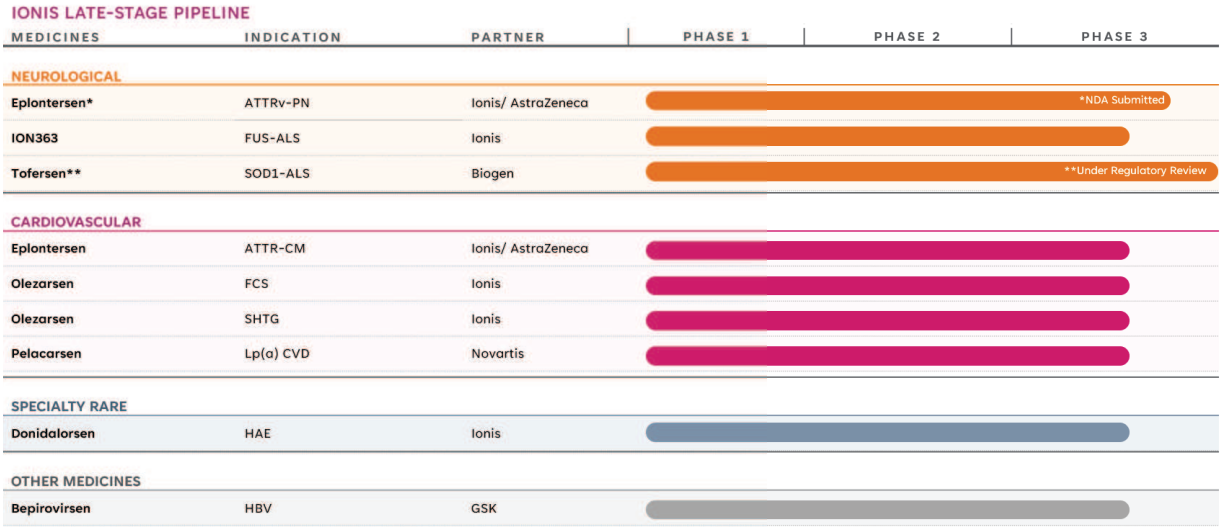
Today, we are a leader in the discovery and development of RNA-targeted therapeutics. We are focused on pioneering new markets and changing standards of care with a focus on cardiovascular and neurological diseases. We also have an emerging specialty rare disease pipeline comprised of medicines that we believe represent compelling opportunities for us. We are building on our capabilities in RNA-targeted therapeutics to achieve our vision to be the leader in genetic medicines.

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



Our Late-Stage Pipeline

We currently have seven medicines in our late-stage pipeline: eplontersen, olezarsen, donidalorsen, ION363, tofersen, pelacarsen and bepirovirsen.



Eplontersen (TTR) – Eplontersen (TTR) – Eplontersen (formerly IONIS-TTR-L_{Rx}) is an investigational LIgand-Conjugated Antisense, or LICA, medicine we designed to inhibit the production of TTR protein. We are developing eplontersen as a monthly self-administered subcutaneous injection to treat all types of ATTR. ATTR

amyloidosis is a systemic, progressive and fatal disease in which patients experience multiple overlapping clinical manifestations caused by the inappropriate formation and aggregation of TTR amyloid deposits in various tissues and organs, including peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to organ failure and eventually death.

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.

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 progressive difficulty with motor functions.

In December 2022, we submitted the eplontersen NDA to the FDA for patients with ATTRv-PN. The eplontersen NDA included results from the interim analysis of the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN. NEURO-TTRansform is a global, multi-center, randomized, open-label study designed to evaluate the efficacy, safety and tolerability of eplontersen. The current study compares to the historical placebo arm from the TEGSEDI (inotersen) NEURO-TTR Phase 3 study. In June 2022, we reported positive interim analysis data from the NEURO-TTRansform study. In the interim analysis, eplontersen 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, eplontersen achieved an 81.2% ($p<0.0001$) mean reduction in the co-primary endpoint of serum TTR concentration compared to baseline, demonstrating reduced TTR protein production. Eplontersen 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 eplontersen significantly improved patient-reported quality of life compared to the external placebo group ($p<0.0001$). Eplontersen had a favorable safety and tolerability profile supportive of continued development.

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 CARDIO-TTRansform study includes co-primary outcome measures of cardiovascular death and frequency of cardiovascular clinical events.

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

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

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

BALANCE is a global, multi-center, randomized, double-blind, placebo-controlled study in approximately 65 patients designed to assess the efficacy, safety and tolerability of olezarsen in patients with FCS. Patients will be treated with 50 mg or 80 mg of olezarsen monthly by subcutaneous injection. The primary endpoint is the percent change from baseline in fasting triglyceride levels at six months compared to placebo.

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 week 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. Additionally, at the highest monthly dose, 91 percent of patients achieved serum triglycerides of ≤ 150 mg/dL, the recognized threshold for cardiovascular risk, compared to less than five percent of patients in the placebo group. Olezarsen also achieved statistical significance in numerous key secondary endpoints, including significant reductions in apoC-III, very low-density lipoprotein cholesterol, or VLDL-C, and remnant cholesterol, and a statistically significant increase in high-density lipoprotein cholesterol, or HDL-C. Olezarsen had a favorable safety and tolerability profile supportive of continued development.

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 target the prekallikrein, or PKK, pathway. 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 November 2021, we initiated the Phase 3 study of donidalorsen, OASIS-HAE, in patients with HAE. OASIS-HAE is a multi-center, randomized, double-blind placebo-controlled study in approximately 80 patients designed to assess the efficacy, safety and tolerability of donidalorsen. Patients will be treated with an 80 mg dose of donidalorsen either every four weeks or every eight weeks by subcutaneous injection. The primary endpoint is the time-normalized number of investigator-confirmed HAE attacks per month from week one to week 25. 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 a Phase 2 clinical study of donidalorsen in patients with HAE. Patients received either donidalorsen 80 mg or placebo subcutaneously once monthly for 17 weeks. The Phase 2 study met its primary and secondary endpoints, achieving significant reductions in the number of attacks suffered by patients with HAE compared to placebo. The study demonstrated a mean reduction of 90 percent in the number of monthly HAE attacks in weeks one to 17 of the study ($p < 0.001$) and a mean reduction of 97 percent in the number of monthly HAE attacks in weeks five to 17 ($p=0.003$). In weeks five to 17, 92 percent of patients treated with donidalorsen were attack-free compared to 0 percent in the placebo group ($p < 0.001$). Additionally, donidalorsen demonstrated an overall reduction in moderate to severe attacks starting with the second dose in the study. For the final month of the study, all donidalorsen treated patients were attack-free. Further, patients reported higher overall health-related quality of life, or HRQoL, over 17 weeks with donidalorsen, with a mean change in total score of the AE-QoL of -26.85, compared with -6.15 in the placebo group ($P=0.002$) where reduction in the score indicates better quality of life. There were improvements observed across all individual domains of the AE-QoL compared with placebo we published. The Phase 3 data were published in the New England Journal of Medicine. Donidalorsen had a favorable safety and tolerability profile supportive of continued development.

In 2022 and in early 2023, we reported positive results from the Phase 2 OLE study of donidalorsen in patients with HAE. Interim data after all patients completed one year of treatment in the study showed a sustained reduction in HAE attacks. Patients completing the Phase 2 study were eligible for enrollment in the OLE study. There were 20 Type 1 or Type 2 HAE patients in the Phase 2 study, and 17 (85%) entered the OLE. Following a 13-week

fixed-dose period where participants received subcutaneous donidalorsen 80 mg every four weeks, eight patients switched to subcutaneous donidalorsen 80 mg every eight weeks. Patients receiving donidalorsen 80 mg every eight weeks experienced a mean reduction in attack rate of 75.6% from baseline and the mean monthly attack rate was 0.28. Six of these patients remained attack free over the one year duration of this analysis, and two of these patients returned to 80 mg every four weeks. For patients treated with donidalorsen, 99.6% of study days were HAE attack-free. Additionally, patients treated for one year with donidalorsen reported a mean improvement of 24 points in their AE-QoL total score across all domains relative to baseline. Donidalorsen had a favorable safety and tolerability profile supportive of continued development.

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

In April 2021, we initiated a Phase 3 study of ION363 in patients with FUS-ALS. The Phase 3 trial of ION363 is a global, multi-center, randomized, double-blind, placebo-controlled study in approximately 75 patients designed to assess the efficacy, safety and tolerability of ION363. Part 1 of the trial consists of patients randomized to receive a loading regimen of ION363 or placebo for weeks one and four followed by one dose every four to 12 weeks for 61 weeks, followed by Part 2, which will be an open-label period in which all patients in the trial will receive ION363 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 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.

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

Tofersen is currently under regulatory review in the U.S. and EU. In July 2022, Biogen announced that the FDA had accepted tofersen's NDA and granted priority review of tofersen for SOD1-ALS. Tofersen has an FDA Advisory Committee meeting planned for March 22, 2023 and a PDUFA date of April 25, 2023. In December 2022, Biogen announced that the EMA accepted the MAA for tofersen for SOD1-ALS.

The tofersen 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 VALOR and the Phase 3 OLE study. The 12-month integrated data show that earlier initiation of tofersen, 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 tofersen (at the start of VALOR) to those who had a delayed initiation of tofersen (six months later, in the OLE).

At the time of the 12-month analysis, because the majority of participants survived without permanent ventilation, or PV, the median time to death or PV and median time to death, could not be estimated. However, early survival data suggest a lower risk of death or PV and death with earlier initiation of tofersen. 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. Tofersen reduced total cerebrospinal fluid, or 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 tofersen, respectively
- 51% and 41% reduction in plasma neurofilament, a marker of neuron injury, respectively

Tofersen had a favorable safety and tolerability profile supportive of continued development.

In April 2021, Biogen initiated a second 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 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.

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 percent 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.

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

HBV infection is a serious health problem that can lead to significant and potentially fatal health conditions, including cirrhosis, liver failure and liver cancer. Chronic HBV infection is one of the most common persistent viral infections in the world, 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 studies will have four stages: (1) a double-blind treatment period of 24 weeks with bepirovirsen or placebo, (2) Nucleoside Analogue, or NA, treatment for 24 weeks, (3) NA cessation with 24 week follow up or (4) continue on NA for 24 weeks, with follow up for a further 24 weeks for patients who stopped NA treatment at week 48. The

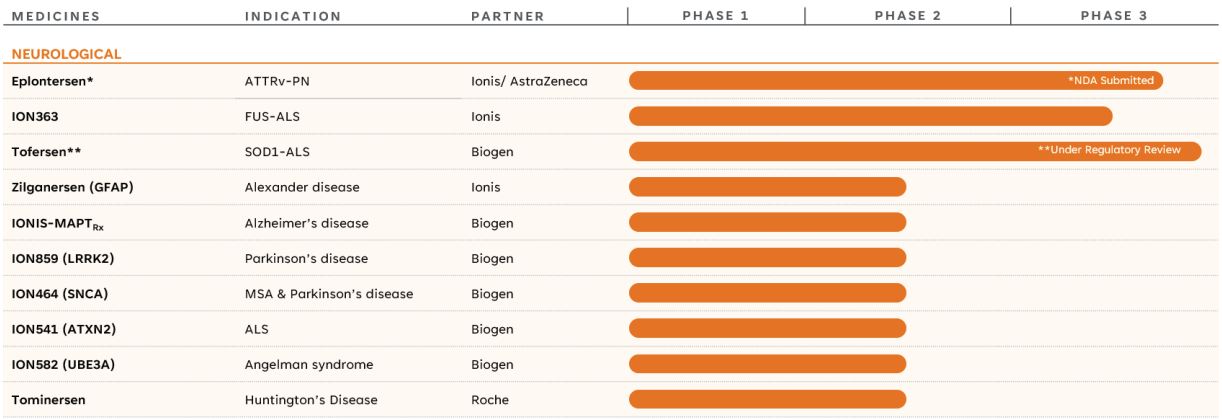
arms will be stratified based on HBsAg levels with the first group including those with HBsAg levels ≥ 100 IU/mL to ≤ 1,000 IU/mL and the second group for those with HBsAg levels >1,000 IU/mL to ≤ 3,000 IU/mL at screening. The primary endpoint is the number of patients achieving functional cure with 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 end of treatment results from the Phase 2b B-CLEAR study of bepirovirsen in patients with chronic HBV infection at the European Association for the Study of the Liver's, or EASL, International Liver Congress. Additionally, in November 2022, GSK presented positive end of study data from the Phase 2b B-CLEAR study at the American Association for the Study of Liver Diseases, or AASLD. The end of study results showed that treatment with bepirovirsen 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, with a loading dose at day four and 11, and at a dose of 300 mg per week for 24 weeks (treatment arm 1), resulted in 9% of patients on NA treatment and 10% of patients not on NA treatment achieving the primary outcome of HBsAg levels below the LLOQ and HBV DNA levels, both below the LLOQ, respectively. This is defined as a sustained response and was observed for 24 weeks post last dose. In the study, sustained response rates were higher in subjects with low baseline HBsAg (< 1000 IU/mL) than in those with high baseline HBsAg (>1000 IU/mL). 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. 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.

Our Neurological Medicines in Development

According to the National Institute of Neurological Disorders and Stroke, or NINDS, at the National Institutes of Health, or NIH, a third of the 7,000 known rare diseases are neurological disorders or thought to include a neurological component. We are currently investigating potential disease-modifying treatments for a broad range of neurological diseases affecting major regions of the brain and in the central nervous system cell types, including ATTRv-PN, ALS and Alzheimer's disease.



Eplontersen – See the medicine description under "Our Late-Stage Pipeline" section above.

ION363 – See the medicine description under "Our Late-Stage Pipeline" section above.

Tofersen – See the medicine description under "Our Late-Stage Pipeline" section above.

Zilganersen – Zilganersen (formerly ION373) is an investigational antisense medicine targeting glial fibrillary acidic protein, or GFAP, mRNA we designed to inhibit the production of GFAP. We are developing zilganersen as

a potential therapy for Alexander disease, or AxD. AxD is a rare, progressive and fatal neurological disease that affects the myelin sheath which protects nerve fibers. AxD is caused by a gain-of-function mutation in the *GFAP* gene and is characterized by progressive deterioration, including loss of skills and independence, generally leading to death in childhood or early adulthood.

Two major types of AxD have been defined. Type I onset typically occurs before 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. The Phase 2/3 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.

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

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

In 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 July 2021, we and Biogen reported positive topline data from our Phase 1/2 study of IONIS-MAPT$_{Rx}$ in patients with mild Alzheimer's disease at the Alzheimer's Association International Conference, or AAIC. The Phase 1/2 study was a blinded, randomized, placebo-controlled, dose-escalation 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 Alzheimer's disease. The study demonstrated robust time and dose dependent lowering of tau protein in cerebrospinal fluid over the three-month treatment period and sustained reductions during the six-month post-treatment period. 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 aggregation of TDP-43, a toxic RNA binding protein found in most patients with ALS, including the approximately 90 percent of the ALS population with no known family history of ALS.

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 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 40 patients designed to assess the safety, tolerability and activity of multiple ascending doses of ION582.

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

Tominersen (HTT) (RG6042) – Tominersen (formerly IONIS-HTT_{Rx}) is an investigational antisense medicine we designed to target the underlying cause of Huntington's disease, or HD, by reducing the production of all forms of the huntingtin protein, or HTT, including its mutated variant, or mHTT. HD is an inherited genetic brain disorder that results in the progressive loss of both mental faculties and physical control. It is caused by the expansion of the 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.

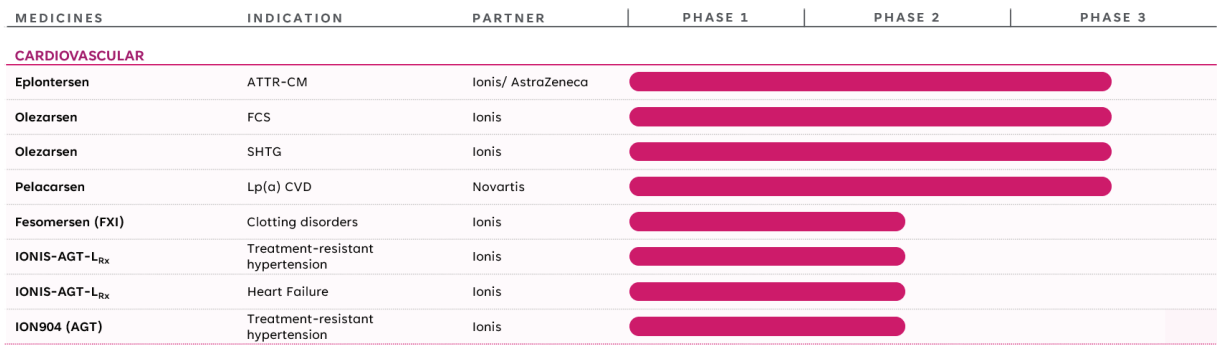
Roche conducted the Phase 3 study, GENERATION HD1, of tominersen in patients with HD. The Phase 3 study was a randomized, multicenter, double-blind, placebo-controlled study that recruited 791 participants. In March 2021,

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 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

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



Eplontersen – See the medicine description under ‘‘Our Late-Stage Pipeline’’ section above.

Olezarsen – See the medicine description under ‘‘Our Late-Stage Pipeline’’ section above.

Pelacarsen – See the medicine description under ‘‘Our Late-Stage 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 American Society of Nephrology’s, or 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.

IONIS-AGT-L_{Rx} – IONIS-AGT-L_{Rx} is an investigational LICA medicine we designed to inhibit the production of angiotensinogen to decrease blood pressure in people with uncontrolled hypertension. Treatment resistant hypertension, or TRH, is defined as failure to achieve a blood pressure goal of 140/90 (systolic/diastolic) despite the use of three or more antihypertensive medications. People with TRH have been found to have a three-fold higher chance of having fatal and non-fatal cardiovascular events relative to those with controlled hypertension.

We are also studying IONIS-AGT-L_{Rx} in patients with chronic heart failure with reduced ejection fraction. Heart failure, or HF, is a chronic, progressive condition in which the heart muscle is unable to pump enough blood to meet the body's needs for blood and oxygen. HF with reduced ejection fraction is a clinical syndrome of shortness of breath, exercise intolerance and/or fluid retention resulting from an impairment of ejection of blood, usually documented by a left ventricular ejection fraction of 40 percent or less on echocardiography.

In January 2021, we initiated a Phase 2b clinical study of IONIS-AGT-L_{Rx} in patients with TRH. The study is a randomized, double-blinded, placebo-controlled study in approximately 150 patients designed to assess the efficacy, safety and tolerability of IONIS-AGT-L_{Rx}. The primary endpoint is the change in systolic blood pressure, or SBP, from baseline.

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

We evaluated IONIS-AGT-L_{Rx} in two randomized, double-blinded, placebo-controlled Phase 2 studies. The first study was in people with mild hypertension and the second was in people with uncontrolled hypertension who were on two or three antihypertensive medications, including ACE inhibitors or ARBs. IONIS-AGT-L_{Rx} significantly reduced AGT levels compared to placebo in both studies. IONIS-AGT-L_{Rx} had a favorable safety and tolerability profile supportive of continued development.

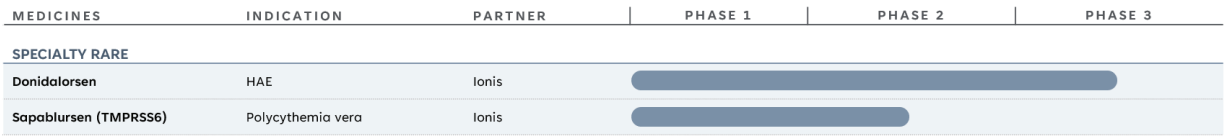
ION904 – ION904 is an investigational next-generation LICA medicine designed to inhibit the production of angiotensinogen to decrease blood pressure in people with uncontrolled hypertension. ION904 is a follow-on medicine targeting AGT, designed to enable less frequent dosing compared to IONIS-AGT-L_{Rx}.

In April 2022, we initiated a 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. The study is a randomized, double-blind, placebo-controlled study in approximately 45 patients designed to assess the safety, tolerability, and efficacy of ION904. The primary endpoint is the percent change in plasma AGT concentration from baseline.

We conducted a Phase 1, blinded, randomized, placebo-controlled, dose-escalation study of ION904 in healthy volunteers that was supportive of continued development.

Specialty Rare Medicines in Development

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



Donidalorsen – See the medicine description under "Our Late-Stage 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.

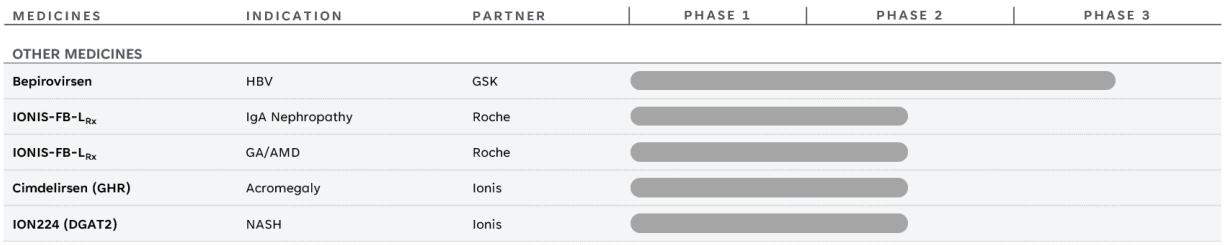
PV is a rare, non-genetic and potentially fatal disease caused by overproduction of red blood cells. This overproduction leads to a thickening of the blood, which increases patients' risk of life-threatening blood clots, including in the lungs, heart and brain. Patients with PV also experience severe iron deficiency due to hepcidin overexpression. 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.

Other Medicines in Development

We also have four medicines in development, outside of our core franchises, of which half are partnered.



Bepirovirsen – See the medicine description under ‘‘Our Late-Stage Pipeline’’ section above.

IONIS-FB-L_{Rx} – IONIS-FB-L_{Rx} (RG6299) 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 immunoglobulin A, or IgA, nephropathy, or IgAN, and geographic atrophy, or 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. AMD is the leading cause of central vision loss in developed countries. GA is an advanced form of AMD.

In November 2022, we presented positive results from the Phase 2 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. IONIS-FB-L_{Rx} had a favorable safety and tolerability profile supportive of continued development. The Phase 2 open-label study remains ongoing and will evaluate IONIS-FB-L_{Rx} in approximately 25 patients with IgAN.

In June 2019, we initiated a Phase 2 study evaluating IONIS-FB-L_{Rx} in patients with GA secondary to age-related macular degeneration. The study is a randomized, masked, placebo-controlled study 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 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.

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

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

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

ION224 (DGAT) – 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 cardiovascular disease, liver cancer, need for liver transplantation and early death. DGAT2 is an enzyme that catalyzes the final step in triglyceride synthesis in the liver. Reducing the production of DGAT2 should therefore decrease triglyceride synthesis in the liver. In animal studies, antisense inhibition of DGAT2 significantly improved liver steatosis, lowered blood lipid levels and reversed diet-induced insulin resistance.

Nonalcoholic fatty liver disease, or NAFLD, describes the full spectrum of liver disease progression from fatty liver to NASH to cirrhosis to hepatocellular carcinoma. NASH epidemiology studies have estimated 13 to 32 percent of the global population has NAFLD, 1.5 to 6.5 percent have NASH, and approximately nine percent 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.

Our Technology

For more than 30 years, we have advanced genetic medicines with the goal to change standards of care and transform the lives of people with devastating diseases. 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 also recently added capabilities to potentially utilize RNA interference, or RNAi, or gene editing in addition to our novel antisense technology, which we believe, gives us the potential to deliver genetic medicines for a greater number of patients in need.

Overview of Antisense 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 eplontersen, 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.

Our advanced LICA technology is a chemical technology we developed that involves attaching a molecule called a ligand that binds with receptors on the surfaces of cells in a highly specific manner. Because these receptors

are often found only on certain cell types, LICA allows us to increase effective delivery of our antisense medicines with higher specificity to certain cell types that express these receptors relative to non-conjugated antisense medicines. 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. In 2022, we reported positive interim analysis data from the NEURO-TTRansform study of eplontersen in patients with ATTRv-PN. Eplontersen demonstrated a favorable safety and tolerability profile with no specific concerns.

Our generation 2.5 chemistry can enable up to 10-fold greater potency compared to our medicines using our Generation 2 chemistries. We can combine our Generation 2.5 chemistry with our LICA technology to further increase potency.

In addition, we are developing LICA conjugation technology that we can use to target tissues other than the liver, such as muscle, and initial results in animals are promising. In the fourth quarter of 2022, we advanced our first program incorporating LICA technology for enhanced delivery to muscle into preclinical development.

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 LICA technology and mesyl phosphoramidate, or MsPA, backbone chemistry. We may also now be able to use RNAi in addition to antisense, in the development of new medicines, depending on which approach demonstrates the best potential product profile for the indication we are pursuing. 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. In the fourth quarter of 2022, we advanced new programs using our MsPA backbone, designed to improve both efficacy and durability, into preclinical development.

Gene Editing and Metagenomi Collaboration

In November 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 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 2022, we recognized $587 million in revenue, the majority of which was from our partnered medicines and programs. We have the potential to earn more than $23 billion in future milestone payments, licensing fees and other payments from our current partnerships. In addition, we are eligible to

receive up to mid-20 percent royalties under 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 7, *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 our technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with SMA. We and Biogen are currently developing numerous investigational medicines to treat neurodegenerative diseases under our collaborations, including medicines in development to treat people with ALS, SMA, AS, Alzheimer's disease and Parkinson's disease. In addition to these medicines, our collaborations with Biogen include a substantial pipeline that addresses a broad range of neurological diseases. From inception through December 31, 2022, we have generated more than $3.5 billion in payments from our Biogen collaborations.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. 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, 2022, we recognized more than $1.8 billion in total revenue under our SPINRAZA collaboration, including nearly $1.4 billion in revenue from SPINRAZA royalties and more than $425 million in R&D revenue.

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a $25 million upfront payment in December 2017. In December 2021, Biogen exercised its option to license ION306, for which we earned a $60 million license fee payment. 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 the collaboration, we are eligible to receive up to $1.2 billion, which is comprised of a $25 million upfront payment, up to $110 million in license fees, up to $80 million in development milestone payments, up to $180 million in regulatory milestone payments and up to $800 million in sales milestone payments and other payments, including up to $555 million if Biogen advances ION306. In addition, we are eligible to receive tiered royalties from the mid-teens to mid-20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration. From inception through December 31, 2022, we have generated $85 million in payments under this collaboration.

Neurology Collaborations

2018 Strategic Neurology

In April 2018, we and Biogen entered into a strategic collaboration agreement 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. Biogen will usually 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.

In June 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at an approximately 25 percent cash premium and $375 million in an upfront payment.

Over the term of the 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 for each medicine that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration. We are currently advancing multiple programs under this collaboration. From inception through December 31, 2022, we have generated nearly $1.1 billion in payments under this collaboration.

2013 Strategic Neurology

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

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed under this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen.

Over the term of the collaboration for tofersen, we are eligible to receive nearly $110 million, which is comprised of a $35 million license fee, up to $18 million in development milestone payments and $55 million in regulatory milestone payments. For each of the other antisense medicines 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, 2022, we have generated more than $300 million under this collaboration, including more than $25 million in milestone payments we received from Biogen in 2022 when Biogen advanced three programs under this collaboration.

2012 Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense medicines to treat neurodegenerative diseases. We are responsible for the development of each of the medicines through the completion of the initial Phase 2 clinical study for such medicine. Biogen has the option to license a medicine from each of the programs through the completion of the first Phase 2 study for each program. Under this collaboration, 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 December 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. Over the term of the collaboration, we are eligible to receive up to $210 million, which is comprised of a $70 million license fee, up to

$10 million in development milestone payments per program and up to $130 million in regulatory milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that Biogen successfully commercializes under this collaboration. From inception through December 31, 2022, we have generated more than $190 million under this collaboration, including nearly $20 million in milestone payments we received from Biogen for advancing ION582 and a $10 million milestone payment we received from Biogen when Biogen advanced IONIS-MAPT$_{Rx}$ during 2022.

Joint Development and Commercialization Arrangement

AstraZeneca

Eplontersen Collaboration

In December 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. We are jointly developing and preparing to commercialize eplontersen with AstraZeneca in the U.S. We granted AstraZeneca exclusive rights to commercialize eplontersen outside the U.S., except certain countries in Latin America.

The collaboration also 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 eplontersen to market outside the U.S.

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, up to $485 million in development and approval milestone payments and up to $2.9 billion in 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 up to the high teens for sales outside the U.S. From inception through December 31, 2022, we have generated more than $275 million in payments under this collaboration, including more than $75 million we earned from cost sharing provisions in 2022.

Research and Development Partners

AstraZeneca

In addition to our collaboration for eplontersen, we have a collaboration with AstraZeneca focused on discovering and developing treatments for cardiovascular, renal and metabolic diseases. In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiovascular, renal and metabolic diseases. Under our collaboration, AstraZeneca has licensed 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 $5.8 billion, which is comprised of a $65 million upfront payment, up to $290 million in license fees, up to $1.1 billion in development milestone payments, up to $2.9 billion in regulatory milestone payments and up to $1.5 billion in sales 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, 2022, we have generated $285 million in payments under this collaboration.

GSK

In March 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. Our collaboration with GSK covers bepirovirsen, an investigational antisense medicine we designed to reduce the production of viral proteins associated with HBV infection. In 2019, following positive Phase 2 results, GSK licensed our HBV program. GSK is responsible for all global development, regulatory and commercialization activities and costs for the HBV program.

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 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, 2022, we have generated more than $50 million in payments under the HBV program collaboration. Subsequent to December 31, 2022, we earned a $15 million milestone payment when GSK initiated a Phase 3 study of bepirovirsen in patients with chronic HBV in January 2023.

Novartis

In January 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, which Novartis initiated in December 2019. In connection with Novartis' license of pelacarsen, we and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of pelacarsen in selected markets. Included in this framework is an option by which Novartis could solely commercialize pelacarsen in exchange for Novartis paying us increased sales milestone payments based on sales of pelacarsen.

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, 2022, we have generated nearly $275 million in payments under this collaboration.

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

Roche

Huntington's Disease

In April 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 December 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen and is now responsible for the global development, regulatory and commercialization activities and costs for tominersen.

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 from any product resulting from this collaboration. From inception through December 31, 2022, we have generated more than $150 million in payments under this collaboration.

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

In October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. We are currently conducting Phase 2 studies in two disease indications for IONIS-FB-L_{Rx}, one for the treatment of patients with GA, the advanced stage of dry AMD, and a second for the treatment of patients with IgA nephropathy. After receiving positive data from the Phase 2 clinical study of IONIS-FB-L_{Rx} in patients with IgAN, Roche licensed IONIS-FB-L_{Rx} in July 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 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, 2022, we have generated more than $130 million under this collaboration, including $55 million in payments we earned in 2022 for advancing IONIS-FB-L_{Rx}.

Commercialization Partnerships

Swedish Orphan Biovitrum AB (Sobi)

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

PTC Therapeutics

In August 2018, we entered into an exclusive license agreement with PTC Therapeutics to commercialize TEGSEDI and WAYLIVRA in Latin America and certain Caribbean countries. Under the license agreement, we are eligible to receive royalties from PTC in the mid-20 percent range on net sales for each medicine. In December 2021, we started receiving royalties from PTC for TEGSEDI sales. We expect to receive royalties from PTC for WAYLIVRA sales starting in 2023.

Technology Enhancement Collaborations

Bicycle Therapeutics License Agreement

In December 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 July 2021, we paid $42 million when we exercised our option to license Bicycle's technology, which included an equity investment in Bicycle. As part of our stock purchase, we entered into a lockup agreement with Bicycle that restricted our ability to trade our Bicycle shares for one year. As a result, we recorded a $7 million equity investment for the shares we received in Bicycle in 2021. We recognized the remaining $35 million as R&D expense in 2021. From inception through December 31, 2022, we have paid Bicycle $47 million under this collaboration agreement.

Metagenomi

In November 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. We will also pay Metagenomi certain fees for the selection of genetic targets, and contingent on the achievement of certain development, regulatory and sales events, milestone payments and royalties. In addition, we will 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.

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

Manufacturing

We manufacture most of the active pharmaceutical ingredient, or API, we use for our research and development activities ourselves. We have also manufactured API and commercial supply for our approved medicines. We have dedicated significant resources to develop ways to improve manufacturing efficiency and capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide medicines, we found that the same techniques we used to efficiently manufacture one oligonucleotide medicine could help improve the manufacturing processes for our other 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. We have begun work on a new manufacturing facility in Oceanside, California that will expand our manufacturing capacity to support our advancing pipeline. Refer to Part I, Item 2, *Properties*, for further discussion of this lease facility.

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 manufacture process performance qualification batches and pre-approval inspection batches of our Phase 3 medicines that may be used for regulatory submissions and, pending regulatory approval, commercial sale. We believe our current network of CMO partners are capable of providing sufficient quantities to meet anticipated commercial demands. Additionally, we continue to evaluate relationships with additional suppliers to increase overall capacity and diversify our supply chain. While we believe that there are alternate sources of supply that can satisfy our commercial requirements, it is possible that identifying and establishing relationships with such sources, if necessary, could result in significant delay or material additional costs. We also could experience a disruption in supply from our current CMO partners.

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

Specifically, we have the following in place for our approved medicines, SPINRAZA, TEGSEDI and WAYLIVRA and our medicines in Phase 3 development.

SPINRAZA

Biogen is responsible for SPINRAZA drug supply.

TEGSEDI and WAYLIVRA

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

Eplontersen

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

Olezarsen, Donidalorsen, ION363

We and/or the CMOs have supplied the API and the finished drug product for olezarsen, donidalorsen and ION363 that we believe will be sufficient through the completion of the Phase 3 programs for each medicine, including process performance qualification batches and pre-approval inspection batches. We plan to leverage our relationships with CMOs to procure long-term raw material and drug supply at competitive prices in the future.

Tofersen

Biogen is responsible for tofersen drug supply, including launch supplies.

Pelacarsen

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

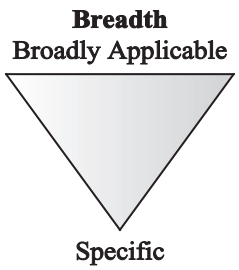
Patents and Proprietary Rights

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

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

Type of Patent Claim
(Broadly Applicable to Specific)

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



Chemically Modified Nucleosides and Oligonucleotides

The most broadly applicable of our patents are those that claim modified nucleosides and oligonucleotides comprising the modified nucleosides that we incorporate into our medicines to increase their therapeutic efficacy. Nucleosides and chemically modified nucleosides are the basic building blocks of our medicines. Therefore, claims that cover any oligonucleotide incorporating one of our proprietary modified nucleosides can apply to a wide array of therapeutic mechanisms of action as well as several therapeutic targets. The following are some of our patents in this category in key jurisdictions (U.S., Europe and Japan):

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

Drug Design Motifs

We also have patents that claim oligonucleotides comprising drug design motifs, or patterns of nucleoside modifications at specified positions in an oligonucleotide. Patent claims covering drug design motifs are independent of nucleic acid sequence, so they cover oligonucleotides having the recited motif, regardless of cellular target or clinical indication. The claimed motifs generally confer properties that optimize oligonucleotides for a particular mechanism of action, such as ribonuclease H (RNase H), RNAi, or splicing. We have designed oligonucleotides incorporating motifs, which we refer to as chimeric compounds or gapmers, to exploit the RNase H mechanism to achieve target RNA reduction. We have patent claims to such antisense drug design motifs incorporating bicyclic nucleosides, which include both locked nucleic acids, or ''LNA'' and cEt. The following patents are some examples of our issued patents in this category in key jurisdictions (U.S., Europe and Japan):

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

LIgand-Conjugated Antisense (LICA) Technology

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

Jurisdiction	Patent 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

Therapeutic Methods of Treatment and Oligonucleotide Drug Sequences

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

SPINRAZA and Survival Motor Neuron

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

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

TEGSEDI and Transthyretin

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

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

WAYLIVRA and Apolipoprotein C-III

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

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

Eplontersen and Transthyretin

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

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

Olezarsen and ApoC-III

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

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

Donidalorsen and PKK

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

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

ION363 and FUS

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

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

Tofersen and SOD-1

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

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

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

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

Manufacturing Patents

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

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

Government Regulation

Regulation by government authorities in the U.S. and other countries is a significant component in the development, manufacture and commercialization of pharmaceutical products and services. In addition to regulations enforced by the FDA and relevant foreign regulatory authorities, we are also subject to regulation under the

Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential future federal, state and local regulations.

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

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

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

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

Both the federal and state governments in the U.S. and foreign governments continue to propose and pass new legislation and regulations designed to contain or reduce the cost of healthcare. For example, in July 2021, the Biden administration released an executive order, ‘‘Promoting Competition in the American Economy,’’ with multiple provisions aimed at prescription drugs. In response to Biden’s executive order, on September 9, 2021, the U.S. Department of Health and Human Services, or HHS, released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. Congress is also considering additional health reform measures 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. It is currently unclear how the IRA will be effectuated but it is likely to have a significant impact on the pharmaceutical industry. 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. In an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation requires manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. Furthermore, 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 we tested and the FDA approved. Such off-label uses are common across medical specialties and often reflect a physician's belief that the off-label use is the best treatment for the patients. The FDA does not regulate the behavior of physicians in their choice of treatments, but FDA regulations do impose stringent restrictions on manufacturers' communications regarding off-label uses. If we do not comply with applicable FDA requirements, we may face adverse publicity, enforcement action by the FDA, corrective advertising, consent decrees and the full range of civil and criminal penalties available to the FDA. Promotion of off-label uses of drugs can also implicate the false claims laws described below.

In the U.S. sales, marketing and scientific/educational programs must also comply with various federal and state laws pertaining to healthcare ''fraud and abuse,'' including anti-kickback laws and false claims laws. Anti-kickback laws make it illegal for a prescription drug manufacturer to solicit, offer, receive, or pay any remuneration in exchange for, or to induce, the referral of business, including the purchase or prescription of a particular drug. Due to the breadth of the statutory provisions, limited statutory exceptions and regulatory safe harbors, and the absence of guidance in the form of regulations and very few court decisions addressing industry practices, it is possible that

our practices might be challenged under anti-kickback or similar laws. Moreover, recent healthcare reform legislation has strengthened these laws. For example, the Patient Protection and Affordable 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. Violations of fraud and abuse laws may be punishable by criminal and civil sanctions, including fines and civil monetary penalties, the possibility of exclusion from federal healthcare programs (including Medicare and Medicaid) and corporate integrity agreements, which impose, among other things, rigorous operational and monitoring requirements on companies. Similar sanctions and penalties also can be imposed upon executive officers and employees, including criminal sanctions against executive officers under the so-called ‘‘responsible corporate officer’’ doctrine, even in situations where the executive officer did not intend to violate the law and was unaware of any wrongdoing.

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

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

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

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 approved medicines and our medicines under development address numerous markets. The diseases our medicines target for which we have or may receive marketing authorization will determine our competition. For some of our medicines, an important factor may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop medicines, complete the clinical trials and marketing authorization processes and supply commercial quantities of the medicines to the market are important competitive factors. We expect to compete with products approved for sale based on a variety of factors, including, among other things, product efficacy, safety, mechanism of action, dosing 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. We do not believe that any medicines meet these criteria to compete with ION363.

SPINRAZA

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

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

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

TEGSEDI and Eplontersen

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

Medicine	Company	Medicine Description[1]	Phase[1]	Route of Administration[1]
Onpattro (Patisiran)	Alnylam	An RNAi medicine formulated with lipid nanoparticles to inhibit TTR mRNA	Approved ATTRv-PN/ Submitted in the U.S. for ATTR-CM	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; Approved in U.S., EU, Japan and select other markets for 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., Submitted in the EU for ATTRv-PN, Phase 3 for ATTR-CM	Subcutaneous Injection
Acoramidis	BridgeBio	Small molecule that binds and stabilizes TTR in the blood	Phase 3 ATTR-CM	Oral

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

WAYLIVRA and Olezarsen

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

Medicine	Company	Medicine Description[(1)]	Phase[(1)]	Route of Administration[(1)]
ARO-APOC3	Arrowhead Pharmaceuticals	Targets APOCIII by utilizing Targeted RNAi Molecule Platform	Phase 3 FCS, Phase 2 SHTG	Subcutaneous Injection
Lomitapide	Amryt Pharma	Microsomal triglyceride transfer protein (MTP) inhibitor	Phase 2 FCS (investigator led)	Oral
Pegozafermin	89bio	FGF21 analog	Phase 2 SHTG	Subcutaneous Injection

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

Donidalorsen

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

Medicine	Company	Medicine Description[(1)]	Phase[(1)]	Route of Administration[(1)]
Takhzyro (lanadelumab-flyo)	Takeda	A monoclonal antibody that inhibits plasma kallikrein activity	Approved for HAE patients 12 years and older	Subcutaneous Infusion
Cinryze (C1 esterase inhibitor)	Takeda	A human plasma protein that mediates inflammation and coagulation	Approved for HAE patients 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 six years and older	Subcutaneous Injection
garadacimab	CSL Behring	An anti-factor XIIa monoclonal antibody	Phase 3	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.

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 Pharmaceuticals	RNAi therapeutic designed to lower Lp(a)	Phase 3	Subcutaneous Injection
SLN360	Silence Therapeutics	RNAi therapeutic designed to lower Lp(a)	Phase 2	Subcutaneous Injection

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

Tofersen

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

Medicine	Company	Medicine Description[(1)]	Phase[(1)]	Route of Administration[(1)]
NI-204	Neurimmune	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.

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We believe there is no medicine in clinical development for FUS-ALS.

Environmental, Social and Governance Initiatives

We recognize the importance of Environmental, Social and Governance, or ESG, initiatives as it relates to our business strategy and risk assessment. During 2021 and 2022, we took steps to formalize our corporate responsibility program and capture and report on the impact of our ESG efforts. In December 2022, we issued our latest corporate responsibility report. As part of our ongoing work, we identified the following corporate responsibility initiatives that we believe are most important to our business:

- Safety of patients in clinical trials;
- Product quality and safety and supply chain management;
- Access to medicines and tackling untreatable diseases;
- Environmental sustainability;
- Human resource management;
- Diversity, equity and inclusion;
- Employee health and safety; and
- Governance and business ethics

We continue to build our corporate responsibility program and ESG framework to support our ongoing commitment to operate our business responsibly and sustainably. In 2022, we established a formal Corporate Responsibility Steering Committee, or Committee, to ensure we develop the right programs and policies to continue to integrate ESG across our organization. Our corporate responsibility initiatives, policies and programs are reviewed on a regular basis by the Committee and its recommendations are key to driving efforts to advance our corporate responsibility strategy to support our growth.

The Committee reports to our Chief Executive Officer and consists of senior leaders in key functions across the company, including legal, finance, human resources and corporate affairs. The Committee is now 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. The Committee periodically updates our executive leadership and the appropriate committees of our Board of Directors on our ongoing ESG efforts.

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 encourage you to view our *2022 Corporate Responsibility Report* published on our website for more detailed information regarding our ESG initiatives. Nothing in the report or on our website shall be deemed incorporated by reference into this Annual Report on Form 10-K.

Employees & Human Capital

As of February 16, 2023, we employed 796 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 2022 was 13 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;
- 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, race, or other personal characteristics. To ensure we are achieving our commitment, we benchmark and evaluate pay based on market data and consider factors such as an employee's role and experience, an employee's performance and internal equity. We also regularly review our compensation practices, in terms of our overall workforce and individual employees, to ensure our pay is fair and equitable.

In 2021, we engaged an independent third-party expert to perform a pay equity analysis that reviewed pay equity by gender, race and age. The results of this analysis did not reveal any pay gaps based on gender, race or age. We plan to continue to engage a third-party expert to review pay equity and report on this analysis as required by future reporting requirements. In 2022, we performed an internal analysis, leveraging our biostatistics team. The analysis showed similar results to the analysis performed in 2021. In addition, we are implementing a comprehensive plan to comply with the new California pay transparency law that went into effect on January 1, 2023.

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 16, 2023:

Name	Age	Position
Brett P. Monia, Ph.D.	61	Chief Executive Officer
Joseph T. Baroldi	45	Executive Vice President, Chief Business Officer
C. Frank Bennett, Ph.D.	66	Executive Vice President, Chief Scientific Officer
Onaiza Cadoret-Manier	58	Executive Vice President, Chief Global Product Strategy and Operations Officer
Richard S. Geary, Ph.D.	65	Executive Vice President, Chief Development Officer
Elizabeth L. Hougen	61	Executive Vice President, Finance and Chief Financial Officer
Patrick R. O'Neil, Esq.	49	Chief Legal Officer, General Counsel and Corporate Secretary
Eugene Schneider, M.D.	50	Executive Vice President, Chief Clinical Development Officer
Eric E. Swayze, Ph.D.	57	Executive Vice President, Research

BRETT P. MONIA, Ph.D.

Chief Executive Officer

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

JOSEPH T. BAROLDI

Executive Vice President, Chief Business Officer

Mr. Baroldi has served as Ionis' Executive Vice President, Chief Business Officer since January 2022. Prior to Ionis, Mr. Baroldi was the chief operating officer at Avidity Biosciences, a biotechnology company focused on oligonucleotide-based therapies. Prior to Avidity, Mr. Baroldi was Vice President, 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.

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 Officer

Dr. Schneider was promoted to Executive Vice President and Chief Clinical Development Officer of Ionis in January 2021. From August 2018 to December 2020, Dr. Schneider served as our Senior Vice President, Head of Clinical Development. From April 2015 to July 2018, Dr. Schneider was our Vice President, Clinical Development,

Severe and Rare Diseases. Dr. Schneider joined Ionis in December 2013 as Executive Director, Clinical Development. Dr. Schneider has two decades of experience in clinical development primarily in the rare diseases space. Prior to joining Ionis, Dr. Schneider was senior medical director at both Synageva BioPharma and Biovail Technologies Ltd.

ERIC E. SWAYZE, Ph.D.

Executive Vice President, Research

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

Item 1A. RISK FACTORS

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

Risks Related to the Commercialization of our Medicines

We have limited experience as a company in commercializing medicines and we will have 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 we will have to invest significant financial and management resources to develop the infrastructure required to successfully commercialize our medicines. There are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel, and effectively manage a geographically dispersed sales and marketing team. We will also need to scale-up existing internal support functions to aid our commercialization efforts, in particular, regulatory affairs and medical affairs. Any failure to effectively build or maintain the infrastructure required to successfully commercialize our medicines, including our sales, marketing, market access, distribution, and related capabilities, or scale-up our existing support functions, could adversely impact the revenue we generate from our medicines. In addition, if we choose to rely on third parties to assist us in commercializing our medicines, we may not be able to enter into collaborations or hire consultants or external service providers on acceptable financial terms, or at all. If we 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 SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, 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 SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, and our medicines in development, economically unviable. If the pricing of any of our medicines decreases for any reason, it will reduce our revenue for such medicine. For example, Biogen has disclosed that SPINRAZA revenue has decreased in part due to lower pricing in the U.S. and certain rest of world markets.

The degree of market acceptance for our medicines, including SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, 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 may develop.

For example, TEGSEDI requires periodic blood and urine monitoring, is available in the U.S. only through a REMS program, and the product label in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis. Our main 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 we or our partner cannot effectively maintain patients on TEGSEDI or WAYLIVRA, including due to limitations or restrictions on the ability to conduct periodic blood and urine monitoring of our patients as a result of the COVID-19 pandemic, we may not be able to generate substantial revenue from TEGSEDI or WAYLIVRA sales.

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

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

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the U.S., no uniform policy of coverage and reimbursement for medicines exists among third-party payers. Therefore, coverage and reimbursement for medicines can differ significantly from payer to payer. For example, the Affordable Care Act, 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, lower out-of-pocket drug costs for patients, and foster scientific innovation to promote better health care and improved health. In addition, the IRA, among other things, allows HHS to negotiate the price of certain single-source drugs covered under Medicare and imposes rebates under Medicare Part B and Medicare Part D. In an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation requires manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. Furthermore, 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. Further, the Biden administration

released an executive order on October 14, 2022, directing HHS to submit a report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. It is unclear whether or how this executive order or similar policy initiatives will be implemented in the future.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Third-party coverage and reimbursement for medicines may not be available or adequate in either the U.S. or international markets, 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 SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, 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 SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, 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 SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen.

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;
- Patisiran, tafamidis, tafamidis meglumine and vutrisiran compete with TEGSEDI and could compete with eplontersen;
- Acoramidis could compete with TEGSEDI and eplontersen;
- ARO-APOC3, lomitapide and pegozafermin could compete with WAYLIVRA and olezarsen;
- Lanadelumab-flyo, C1 esterase inhibitor, berotralstat, C1 esterase inhibitor subcutaneous, garadacimab, and NTLA-2002 could compete with donidalorsen;
- Olpasiran and SLN360 could compete with pelacarsen; and
- NI-204 could compete with tofersen.

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

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

Our medicines could be subject to regulatory limitations following approval.

Following approval of a medicine, we and our partners must comply with comprehensive government regulations regarding the manufacture, marketing and distribution of medicines. Promotional communications regarding prescription medicines must be consistent with the information in the product's approved labeling. We or our partners may not obtain the labeling claims necessary or desirable to successfully commercialize our medicines, including SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, 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 agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, when approved, the FDA or a foreign regulatory authority may condition approval on the performance of post-approval clinical studies or patient monitoring, which could be time consuming and expensive. For example, in connection with the conditional marketing approval for WAYLIVRA in the EU, we are required to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. If the results of such post-marketing studies are not satisfactory, the FDA, EC or other foreign regulatory 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 manufacturers or our partners fail to comply with regulatory requirements, we or our partners may, among other things, lose regulatory approval and be forced to withdraw products from the market, need to conduct additional clinical studies, incur restrictions on the marketing, distribution or manufacturing of the product, and/or change the labeling of our medicines.

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

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

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

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

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

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

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

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

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. To that end, we have begun work on a new manufacturing facility in Oceanside, California that will expand our manufacturing infrastructure. We will incur substantial expenditures to build our new manufacturing facility and, following its completion, will likely need to hire and train additional staff to operate the facility. 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 SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, and our medicines in development, or could result in enforcement action after authorization that might limit the commercial success of our medicines, including SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, and our medicines in development.

We rely on third-party manufacturers to supply the drug substance and drug product for TEGSEDI and drug product for WAYLIVRA. Any delays or disruption to our own or third-party commercial manufacturing capabilities, including any interruption to our supply chain as a result of the COVID-19 pandemic or the ongoing war between Russia and Ukraine, could limit the commercial success of our medicines.

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

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

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

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

Risks Related to the Development and Regulatory Approval of our Medicines

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

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

We and our partners may not obtain necessary regulatory approvals on a timely basis, if at all, for our medicines. It is possible that regulatory agencies will not approve our medicines for marketing or SPINRAZA, TEGSEDI or WAYLIVRA in additional markets or for additional indications. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of any of our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or our medicines in development, the agency will not approve the specific medicine or will require additional studies, which 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 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, or may delay the inspection of such facilities due to restrictions related to the COVID-19 pandemic; and
- the approval policies or regulations of such authorities or their prior guidance to us or our partners during clinical development may significantly change in a manner rendering our clinical data insufficient for approval.

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

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

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

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

There are a number of factors that could cause a clinical study to fail or be delayed, including:

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

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

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

Any failure or delay in our clinical studies, including the studies of donidalorsen, eplontersen, ION363, olezarsen, pelacarsen and tofersen, 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 donidalorsen, eplontersen, ION363, olezarsen, pelacarsen and tofersen. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees, 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 are experiencing labor shortages, which could impact their ability to perform services for us for certain of our clinical trials. The failure of these third parties to carry out their obligations, including as a result of delays or disruptions caused by the COVID-19 pandemic, or a termination of our relationship with such third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines or additional marketing authorizations for TEGSEDI and WAYLIVRA.

In addition, while we do not have any clinical trial sites in Ukraine, we do have a limited number of clinical trial sites in Russia and surrounding countries that may be impacted by the ongoing war between Russia and Ukraine 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 eplontersen;
- Novartis for development and funding of pelacarsen;
- Biogen for development and funding of tofersen;
- Biogen for additional studies of SPINRAZA; and
- GSK for development and funding of bepirovirsen.

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, 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, 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 SPINRAZA, eplontersen, pelacarsen and tofersen.

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

In the U.S., under the Orphan Drug Act, the FDA may designate a medicine as an orphan drug if it is intended to treat a rare disease or condition affecting fewer than 200,000 individuals in the U.S. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods. The FDA has granted orphan drug designation to eplontersen for the treatment of patients with transthyretin-mediated amyloidosis and to ION582 for the treatment of patients with Angelman syndrome. The FDA and EMA have granted orphan drug designation to TEGSEDI for the treatment of patients with ATTRv-PN, to WAYLIVRA for the treatment of patients with FCS, and to tominersen for the treatment of patients with HD. In addition, the EMA has granted orphan drug designation to WAYLIVRA for the treatment of patients with FPL. Even if approval is obtained on a medicine that has been designated as an orphan drug, we may lose orphan drug exclusivity if the FDA or EMA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable medicine to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain

approval for the same medicine in a safer or more effective form or that makes a major contribution to patient care. If we lose orphan drug exclusivity on any of our medicines, we may face increased competition and lose market share for such medicine.

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 build-out of a new manufacturing facility. All of these activities will require significant cash. As of December 31, 2022, we had cash, cash equivalents and short-term investments equal to $2.0 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including SPINRAZA, TEGSEDI and WAYLIVRA, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors such as:

- successful commercialization of SPINRAZA, TEGSEDI and WAYLIVRA;
- the profile and launch timing of our medicines, including donidalorsen, eplontersen, ION363, olezarsen, pelacarsen and tofersen;
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical studies;
- the time and costs involved in obtaining marketing authorizations;
- competing technological and market developments, including the introduction by others of new therapies that address our markets; and
- our manufacturing requirements and capacity to fulfill such requirements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available 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. 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, 2022, we had an accumulated deficit of approximately $1.4 billion and stockholders' equity of approximately $0.6 billion. Most of our historical losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our income has 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 SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, or any of our medicines in development as patentable. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method-of-use patents, the practice is common and such infringement is difficult to prevent, even through legal action.

If we or any licensor partner loses or cannot obtain patent protection for SPINRAZA, TEGSEDI, WAYLIVRA, eplontersen and tofersen, 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 SPINRAZA, TEGSEDI and WAYLIVRA, and our medicines in development. We have clinical study insurance coverage and commercial product liability insurance coverage. However, this insurance coverage may not be adequate to cover claims against us, or be available to us at an acceptable cost, if at all. Regardless of their merit or eventual outcome, product liability claims may result in decreased demand for our medicines, injury to our reputation, withdrawal of clinical study volunteers and loss of revenues. Thus, whether or not we are insured, a product liability claim or product recall may result in losses that could be material.

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. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. In addition, failure to succeed in clinical studies may make it more challenging to recruit and retain qualified scientific personnel.

Risks related to the COVID-19 pandemic and other events

Our business may be adversely affected by pandemics, climate change, extreme weather events, earthquakes, war, 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, some physician and hospital policies that were put in place as a result of the COVID-19 pandemic restricted in-person access by third parties, which in some cases impacted our commercialization efforts for TEGSEDI and WAYLIVRA. In addition, in December 2021, Novartis announced that enrollment for the Phase 3 HORIZON study had been delayed due to the COVID-19 pandemic. The COVID-19 pandemic continues to evolve, and while we believe we have not experienced material adverse effects to our business as a result of the COVID-19 pandemic, the ultimate impact of the COVID-19 pandemic or a similar health epidemic is highly uncertain.

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 and will move such manufacturing to our new facility in Oceanside, California once it is built. We manufacture the finished drug product for TEGSEDI and WAYLIVRA at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA. The facilities and the equipment we, our partners and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace. Our facilities or those of our partners or contract manufacturers may be harmed by natural disasters or other events outside our control, such as earthquakes, war, civil or political unrest, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, and if such facilities are affected by a disaster or other event, our development and commercialization efforts would be delayed. Although we possess property damage and business interruption

insurance coverage, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

Risks related to cybersecurity

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

We are dependent upon our own and third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity, with third-party phishing and social engineering attacks in particular increasing during the COVID-19 pandemic. 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 war between Russia and Ukraine, as a result of which several companies (not including us) have reported recent cybersecurity events.

Cyber-attacks could include the deployment of harmful malware, denial-of-service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our business partners face similar risks and any security breach of their systems could adversely affect our security posture. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and state breach notification laws and foreign law equivalents, subject us to financial penalties and mandatory and costly corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation or other liability under laws and regulations that protect personal data, any of which could disrupt our business and result in increased costs or loss of revenue. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, our efforts may not prevent service interruptions or identify breaches in our systems that could adversely affect our business and operations and result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us.

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, including the impacts of the COVID-19 pandemic. If we do not achieve milestones in accordance with our or our investors' or securities analysts' expectations, including milestones related to SPINRAZA, TEGSEDI, WAYLIVRA, donidalorsen, eplontersen, ION363, olezarsen, pelacarsen and tofersen, 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, 2022, the market price of our common stock ranged from $48.82 to $28.25 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, the COVID-19 pandemic caused a significant disruption of global financial markets and resulted in increased volatility in the trading price of our common stock. The global credit and financial markets may also be adversely affected by the ongoing war between Russia and Ukraine and measures taken in response thereto. 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, convertible notes documents, call spread hedge transaction documents and Delaware law may prevent stockholders from receiving a premium for their shares.

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

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

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

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

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

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

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

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

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

The global credit markets, the financial services industry, the U.S. capital markets, and the U.S. economy as a whole have recently experienced substantial turmoil and uncertainty characterized by unprecedented intervention by the U.S. federal government in response to the COVID-19 pandemic. While the potential economic impact brought by, and the duration of, the COVID-19 pandemic may be difficult to assess or predict, it could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and has and could continue to affect the value of our securities. In addition, the global credit and financial markets may be adversely affected by the ongoing war between Russia and Ukraine and measures taken in response thereto. In the past, the failure, bankruptcy, or sale of various financial and other institutions created similar turmoil and uncertainty in such markets and industries. It is possible that a similar crisis in the global credit markets, the U.S. capital markets, the financial services industry or the U.S. economy may adversely affect our business, vendors and prospects, as well as our liquidity and financial condition. Additionally, our insurance carriers and insurance policies covering all aspects of our business may become financially unstable or may not be sufficient to cover any or all of our losses and may not continue to be available to us on acceptable terms, or at all. In addition, due to the rapidly rising inflation rate, we may experience significantly increased costs of goods and services for our business.

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

- compliance with differing or unexpected regulatory requirements for our medicines and foreign employees;
- complexities associated with managing multiple payer reimbursement regimes, government payers or patient self-pay systems;
- difficulties in staffing and managing foreign operations;
- in certain circumstances, increased dependence on the commercialization efforts and regulatory compliance of third-party distributors or strategic partners;
- foreign government taxes, regulations and permit requirements;

- U.S. and foreign government tariffs, trade restrictions, price and exchange controls and other regulatory requirements;
- anti-corruption laws, including the Foreign Corrupt Practices Act, or the FCPA, and its equivalent in foreign jurisdictions;
- economic weakness, including inflation, natural disasters, war, events of terrorism, political instability or public health issues or pandemics, such as the COVID-19 pandemic, in particular foreign countries or globally;
- fluctuations in currency exchange rates, which could result in increased operating expenses and reduced revenue, and other obligations related to doing business in another country;
- compliance with tax, employment, privacy, immigration and labor laws, regulations and restrictions for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the U.S.; and
- changes in diplomatic and trade relationships.

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

Risks related to compliance with laws

Our operations are subject to additional healthcare laws.

Our operations are subject to additional healthcare laws, including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws, which are subject to change at any time. 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 carryforward our NOLs to offset our future taxable income, if any, until such NOLs are used or expire. The same is true of other unused tax attributes, such as tax credits.

Under the current U.S. federal income tax law, U.S. federal NOLs generated in taxable years beginning after December 31, 2017 may be carried forward indefinitely, but the deductibility of such U.S. federal NOLs is limited to 80 percent of taxable income. It is uncertain if and to what extent various states will conform to current U.S. federal income tax law, and there may be periods during which states suspend or otherwise limit the use of NOLs for state income tax purposes.

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

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

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

We could be subject to additional tax liabilities.

We are subject to U.S. federal, state, local and foreign income taxes, sales taxes in the U.S., withholding taxes and transaction taxes in foreign jurisdictions. Significant judgment is required in evaluating our tax positions and our

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

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

As of February 16, 2023, 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 and storage space facility	Carlsbad, CA	18,700	Leased	2023	None
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
		341,700			

In October 2022, we concurrently entered into two purchase and sale agreements with a real estate investor. Under the agreements, we sold and leased back the facilities at our headquarters location in Carlsbad, California and will sell, subject to meeting certain closing conditions, two lots of undeveloped land adjacent to our headquarters. We sold the facilities at our headquarters for net proceeds of approximately $200 million, with the potential to receive additional payments of up to $40 million plus funding to expand our R&D campus. We used a portion of the sale proceeds to extinguish our mortgage debt on our headquarters facilities of $51 million. 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. In connection with the sale of our two undeveloped lots, we will enter 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 research and development space and office space. We will design and construct tenant improvements to customize the facility's interior space. Once this new facility is completed, our lease will commence.

In October 2022, we entered into a build-to-suit lease agreement to lease a development chemistry and manufacturing facility in Oceanside, California. The lessor will develop and construct a 217,000-square-foot building, composed of manufacturing space, office space, research and development space and warehouse 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 20 years and 3 months with options to extend the lease for two additional terms of 10 years each. The lease will commence when the lessor's construction is complete and we are able to begin constructing tenant improvements.

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

Item 3. Legal Proceedings

For details of legal proceedings, refer to Part IV, Item 15, Note 9, *Legal Proceedings,* in the Notes to the Consolidated Financial Statements.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

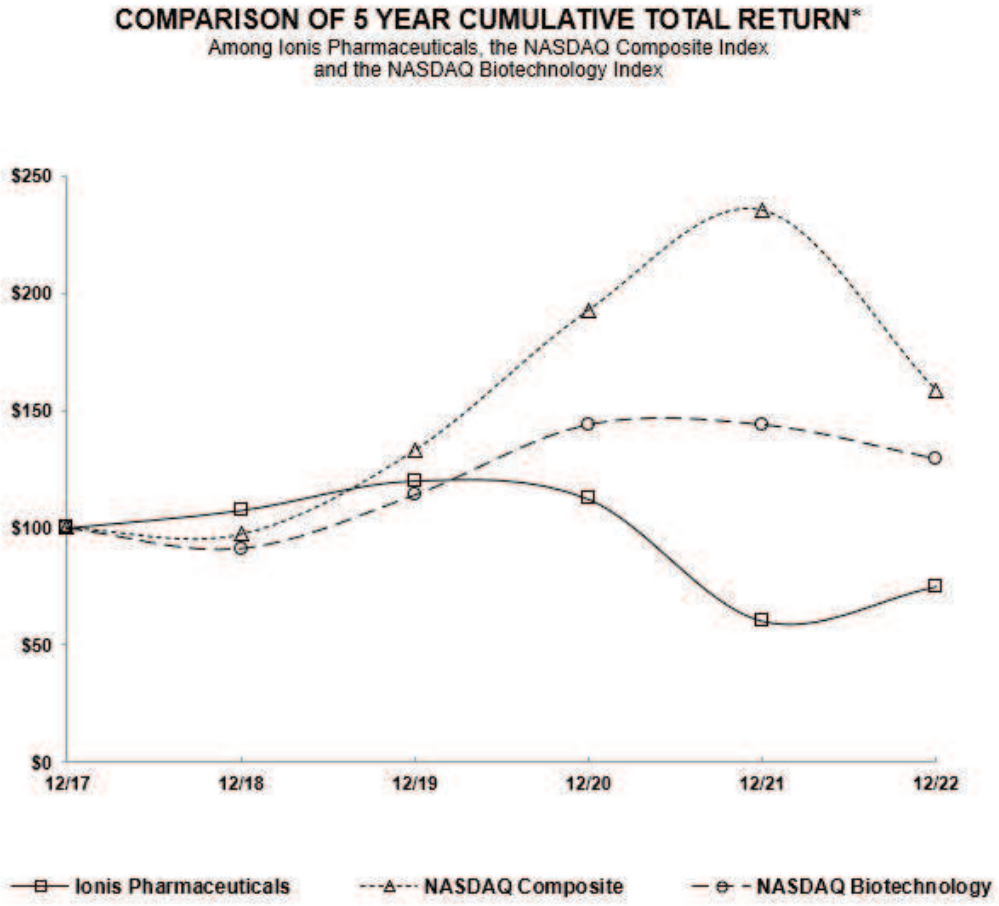
Market Information and Dividends

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol ''IONS.'' As of February 16, 2023, there were approximately 483 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, 2017 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, 2017 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-17	Dec-18	Dec-19	Dec-20	Dec-21	Dec-22
Ionis Pharmaceuticals, Inc.	$100.00	$107.48	$120.10	$112.41	$ 60.50	$ 75.09
Nasdaq Composite Index	$100.00	$ 97.16	$132.81	$192.47	$235.15	$158.65
Nasdaq Biotechnology Index	$100.00	$ 91.14	$114.02	$144.15	$144.18	$129.59

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

Item 6. Selected Financial Data

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

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

This financial review presents our operating results for each of the two years in the period ended December 31, 2022, and our financial condition as of December 31, 2022. Refer to our 2021 Form 10-K for our results of operations for 2021 compared to 2020. 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, we were founded over 30 years ago to deliver innovative new medicines for diseases with great medical need. Today, we are building on our advancements in RNA-targeted therapeutics with a vision to be the leader in genetic medicines. We believe our genetic medicines have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases. We currently have three marketed medicines: SPINRAZA, TEGSEDI and WAYLIVRA. We also have two medicines, eplontersen and tofersen, that will add to our commercial portfolio this year, assuming positive regulatory outcomes. In addition to our commercial medicines and medicines under regulatory review, we have a rich innovative late- and mid-stage pipeline primarily focused on our leading cardiovascular and neurology franchises. We currently have seven medicines in Phase 3 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 2022 compared to 2021. Refer to our 2021 Form 10-K for our results of operations for 2021 compared to 2020. The following table provides selected summary information from our consolidated statements of operations for 2022 and 2021 (in millions):

	Year Ended December 31,	
	2022	2021
Total revenue	$ 587.4	$ 810.5
Total operating expenses	$ 997.6	$ 840.6
Loss from operations	$ (410.2)	$ (30.2)
Net loss	$ (269.7)	$ (28.6)
Cash, cash equivalents and short-term investments	$1,986.9	$2,115.0

Revenue

Total revenue for 2022 was $587.4 million compared to $810.5 million in 2021 and was comprised of the following (in millions):

	Year Ended December 31,	
	2022	2021
Revenue:		
Commercial revenue:		
SPINRAZA royalties	$242.3	$267.8
TEGSEDI and WAYLIVRA revenue, net.	30.1	55.5
Licensing and other royalty revenue	31.0	19.1
Total commercial revenue	303.4	342.4
R&D revenue:		
Amortization from upfront payments	68.6	77.5
Milestone payments	74.0	88.3
License fees	37.0	291.3
Other services	27.6	11.0
Collaborative agreement revenue	207.2	468.1
Eplontersen joint development revenue	76.8	—
Total R&D revenue	284.0	468.1
Total revenue	$587.4	$810.5

Our 2022 revenue continued to be derived from diverse sources, with just over half coming from commercial products and the balance from numerous partnered programs. SPINRAZA royalties, the largest contributor to our commercial revenue, increased each quarter in 2022. Total SPINRAZA product sales increased six percent in the fourth quarter of 2022 compared to the third quarter of 2022 and also increased four percent compared to the same quarter in 2021. The increases were driven by stabilization in the U.S. and growth in Asian markets, partially offset by competition in Europe. Total SPINRAZA product sales decreased six percent year-over-year driven by foreign currency exchange and competition in Europe, partially offset stabilization in the U.S. and growth in Asian markets. Our TEGSEDI and WAYLIVRA revenue was also lower year-over-year due to the shift to distribution fees in 2021.

Our R&D revenue for 2022 included $112 million from Biogen for advancing several neurology disease programs, $77 million from AstraZeneca for its share of the global Phase 3 development costs for eplontersen and $64 million from Roche for licensing and advancing IONIS-FB-L_{Rx}, among other partnered payments. R&D revenue was higher in 2021 compared to 2022 driven primarily by the $200 million we earned in the fourth quarter of 2021 from AstraZeneca to jointly develop and commercialize eplontersen.

Eplontersen Collaboration with AstraZeneca

Our financial results for the year ended December 31, 2022 reflected the cost-sharing provisions related to our collaboration with AstraZeneca to develop and commercialize eplontersen 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. In the year ended December 31, 2022, we earned $77 million in joint development revenue and recorded $147M of R&D expenses related to Phase 3 development expenses under this collaboration.

As AstraZeneca is responsible for the majority of the medical affairs and commercial costs in the U.S. and all costs associated with bringing eplontersen 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. In the year ended December 31, 2022, we recognized $2.0 million and $2.6 million of medical affairs expenses and commercialization expenses for eplontersen, respectively, net of cost-share funding from AstraZeneca. We expect our medical affairs and commercialization expenses to increase as eplontersen advances toward the market under our collaboration with AstraZeneca.

The following is a summary of the financial impacts on our statement of operations for the year ended December 31, 2022 of the joint development activities under our eplontersen collaboration with AstraZeneca:

Operating Expenses

Our operating expenses were as follows (in millions):

	Year Ended December 31,	
	2022	2021
Operating expenses, excluding non-cash compensation expense related to equity awards	$897.3	$696.0
Restructuring expenses	—	23.9
Total operating expenses, excluding non-cash compensation expense related to equity awards	897.3	719.9
Non-cash compensation expense related to equity awards	100.3	120.7
Total operating expenses	$997.6	$840.6

Our operating expenses, excluding non-cash compensation expense related to equity awards, increased in 2022 compared to 2021. Our R&D expenses increased in 2022 compared to 2021 due to our investments in advancing our late-stage pipeline, including the expanded number of Phase 3 studies we are conducting, which doubled from three to six studies in 2021. Our R&D expenses also increased in 2022 compared to 2021 due to $80 million that we recognized in 2022 for licensing Metagenomi's gene editing technologies. Our SG&A expenses decreased in 2022 compared to 2021 as a result of savings we realized from integrating Akcea and restructuring our commercial operations for TEGSEDI and WAYLIVRA, partially offset by the increase in expenses related to our go-to-market activities for eplontersen, donidalorsen and olezarsen.

Our non-cash compensation expense related to equity awards decreased in 2022 compared to 2021 as a result of the decrease in our stock price in 2022 compared to 2021 and reduced headcount due to restructuring our commercial operations in 2021. We anticipate our non-cash compensation expense related to equity awards to increase in 2023 due to increased headcount and an increase in our stock price when we granted annual equity awards to our employees in January 2023 compared to January 2022.

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.

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

	Year Ended December 31,	
	2022	2021
Cost of sales, excluding non-cash compensation expense related to equity awards	$13.4	$10.4
Non-cash compensation expense related to equity awards	0.7	0.4
Total cost of sales	$14.1	$10.8

Research, Development and Patent Expenses

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

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

	Year Ended December 31,	
	2022	2021
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$759.4	$547.4
Restructuring expenses	—	8.5
Total research, development and patent expenses, excluding non-cash compensation expense related to equity awards	759.4	555.9
Non-cash compensation expense related to equity awards	73.7	87.6
Total research, development and patent expenses	$833.1	$643.5

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.

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

	Year Ended December 31,	
	2022	2021
Drug discovery expenses, excluding non-cash compensation expense related to equity awards	$181.3	$136.6
Non-cash compensation expense related to equity awards	16.2	21.4
Total drug discovery expenses	$197.5	$158.0

Drug discovery expenses, excluding non-cash compensation expense related to equity awards, increased in 2022 compared to 2021 primarily due to $80 million that we recognized in 2022 for licensing Metagenomi's gene editing technologies. In 2021, we incurred certain licensing expenses, including $35 million for licensing Bicycle Therapeutics' peptide technology.

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,	
	2022	2021
TEGSEDI and WAYLIVRA	$ 10.6	$ 8.3
Eplontersen	103.9	79.1
Olezarsen	68.1	22.0
Donidalorsen	14.1	6.7
ION363	8.4	7.7
Other development projects	129.1	104.5
Development overhead expenses	92.0	75.2
Restructuring expenses	—	7.7
Total drug development, excluding non-cash compensation expense related to equity awards	426.2	311.2
Non-cash compensation expense related to equity awards	31.5	37.8
Total drug development expenses	$457.7	$349.0

Our development expenses, excluding non-cash compensation expense related to equity awards, increased in 2022 compared to 2021 primarily due to our advancing late-stage pipeline, including the expanded number of Phase 3 studies we are conducting, which doubled over the course of 2021 from three to six 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. And, 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 managing publications planning, funding and coordinating investigator-sponsored trials and communicating scientific and clinical information to healthcare providers, medical professionals and patients.

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

	Year Ended December 31,	
	2022	2021
Medical affairs expenses, excluding non-cash compensation expense related to equity awards	$15.9	$11.6
Non-cash compensation expense related to equity awards	2.0	1.4
Total medical affairs expenses	$17.9	$13.0

Medical affairs expenses, excluding non-cash compensation expense related to equity awards, increased in 2022 compared to 2021 due to increased costs we incurred as we built our medical affairs function to support 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, 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.

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

	Year Ended December 31,	
	2022	2021
Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	$76.2	$47.2
Restructuring expenses	—	0.8
Total manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards	76.2	48.0
Non-cash compensation expense related to equity awards	9.9	11.5
Total manufacturing and development chemistry expenses	$86.1	$59.5

Manufacturing and development chemistry expenses, excluding non-cash compensation expense related to equity awards, increased in 2022 compared to 2021 due to increased R&D-related manufacturing costs we incurred in preparation for our near-term commercial launches of eplontersen, 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, informatics costs, procurement costs and waste disposal costs. We call these costs R&D support expenses.

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

	Year Ended December 31,	
	2022	2021
Personnel costs	$21.2	$17.7
Occupancy	19.2	13.1
Patent expenses	4.7	5.3
Insurance	3.8	3.2
Computer software and licenses	1.9	1.8
Other	9.0	7.3
Restructuring expenses	—	0.1
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	59.8	48.5
Non-cash compensation expense related to equity awards	14.1	15.5
Total R&D support expenses	$73.9	$64.0

R&D support expenses, excluding non-cash compensation expense related to equity awards, increased in 2022 compared to 2021. The increase was primarily related to increased occupancy and personnel 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

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

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

	Year Ended December 31,	
	2022	2021
Selling, general and administrative expenses, excluding non-cash compensation expense related to equity awards	$124.4	$138.1
Restructuring expenses	—	15.4
Total selling, general and administrative expenses, excluding non-cash compensation related to equity awards	124.4	153.5
Non-cash compensation expense related to equity awards	25.9	32.8
Total selling, general and administrative expenses	$150.3	$186.3

SG&A expenses, excluding non-cash compensation expense related to equity awards, decreased in 2022 compared to 2021 due to operating efficiencies achieved from restructuring our commercial operations for TEGSEDI and WAYLIVRA, partially offset by increased expenses for our go-to-market preparations for our near-term commercial opportunities. Non-cash compensation expense related to equity awards decreased in 2022 compared to 2021 as a result of restructuring our commercial operations for TEGSEDI and WAYLIVRA in 2021.

Investment Income

Investment income for 2022 was $25.3 million compared to $10.0 million for 2021. The increase in investment income was primarily due to an increase in interest rates during 2022 compared to 2021.

Interest Expense

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

	Year Ended December 31,	
	2022	2021
Convertible senior notes:		
Non-cash amortization of the debt discounts and debt issuance costs	$5.3	$4.9
Interest expense payable in cash	0.7	1.9
Interest on mortgage for primary R&D and manufacturing facilities	2.1	2.5
Total interest expense	$8.1	$9.3

Gain (Loss) on Investments

We recorded a $7.3 million loss on investments for 2022 compared to a $10.1 million gain on investments for 2021. The period-over-period fluctuation in our gain (loss) on investments was primarily driven by changes in fair value of our investments in publicly traded biotechnology companies.

Gain on Sale of Real Estate

In October 2022, we concurrently entered into two purchase and sale agreements with a real estate investor. Under the agreements, we sold and leased back the facilities at our headquarters location in Carlsbad, California and will sell, subject to meeting certain closing conditions, two lots of undeveloped land adjacent to our headquarters. We sold the facilities at our headquarters for a total purchase price of $263.4 million and recorded a gain of $150.1 million in the fourth quarter of 2022, resulting in income tax expense of $8.8 million.

Other Expense

In 2022, we recorded a $7.7 million net expense to settle a litigation claim.

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

Income Tax Expense (Benefit)

We recorded an income tax expense of $11.7 million for 2022 compared to an income tax benefit of $0.6 million for 2021. Beginning in 2022, the Tax Cuts and Jobs Act of 2017, or TCJA, requires taxpayers to capitalize and amortize research and development expenditures pursuant to Internal Revenue Code, or IRC, Section 174. Our 2022 tax expense relates primarily to the impact of this new law and to federal and state tax on the gain from the sale of our headquarters facilities that closed in October 2022.

Net Loss and Net Loss per Share

We generated a net loss of $269.7 million for 2022 compared to $28.6 million for 2021. Our net loss increased for 2022 compared to 2021 primarily due to decreased revenue and increased expenses year-over-year, as discussed in the revenue and expenses sections, respectively.

Basic and diluted net loss per share for 2022 were each $1.90. Basic and diluted net loss per share for 2021 were each $0.20.

Liquidity and Capital Resources

We have financed our operations primarily from research and development collaborative agreements. We also finance our operations from commercial revenue from SPINRAZA royalties and TEGSEDI and WAYLIVRA commercial revenue. From our inception through December 31, 2022, we have earned approximately $6.4 billion in revenue. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From the time we were founded through December 31, 2022, we have raised net proceeds of approximately $2.0 billion from the sale of our equity securities. Additionally, we borrowed approximately $2.1 billion under long-term debt arrangements to finance a portion of our operations over the same time period.

Our cash, cash equivalents and short-term investments, debt obligations and working capital decreased from 2021 to 2022. In 2021, we issued $632.5 million of 0% Notes (due in April 2026) and we used a portion of the proceeds to repurchase $247.9 million of our 1% Notes in April 2021. We paid the remaining principal balance of our 1% Notes with $62.0 million of cash at maturity in November 2021. In 2022, we sold the facilities and related land at our headquarters for a total purchase price of $263.4 million and used a portion of the proceeds to extinguish our mortgage debt on these facilities of $51.3 million. At December 31, 2022, we had $2.0 billion of cash and short-term investments on hand. We believe our cash and short-term investment balance is sufficient to fund our operations in the short-term and in the longer-term. In 2022, our working capital decreased because our cash and investments decreased as discussed above.

The following table summarizes our contractual obligations as of December 31, 2022. The table provides a breakdown of when obligations become due. We provide a more detailed description of the major components of our debt in Note 4, *Long-Term Obligations and Commitments*.

Contractual Obligations (selected balances described below)	Payments Due by Period (in millions)		
	Total	Less than 1 year	More than 1 year
0% Notes (principal payable)	$ 632.5	$ —	$ 632.5
0.125% Notes (principal and interest payable)	550.2	0.7	549.5
Building mortgage payments (principal and interest payable)	10.7	0.5	10.2
Operating leases	299.6	20.1	279.5
Other obligations (principal and interest payable)	0.9	0.1	0.8
Total	$1,493.9	$21.4	$1,472.5

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. Due to the uncertainty with respect to the timing of future cash flows associated with our unrecognized tax benefits, we are unable to make reasonably reliable estimates of the period of cash settlement with the respective taxing authorities. Therefore, we have excluded our gross unrecognized tax benefits from our contractual obligations table above. We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

Convertible Debt and Call Spread

Refer to our Convertible Debt and Call Spread accounting policies in Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, and Note 4, *Long-Term Obligations and Commitments*, in the Notes to our consolidated financial statements for the significant terms of each convertible debt instrument.

Operating Facilities

Refer to Part IV, Item 15, Note 4, *Long-Term Obligations and Commitments*, in the Notes to our consolidated financial statements for further details on our operating facilities.

Operating Leases

Refer to Part IV, Item 15, Note 4, *Long-Term Obligations and Commitments*, in the Notes to our 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 4, *Long-Term Obligations and Commitments*, in the Notes to our 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, 2022 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 that could provide for additional revenue to us and we may incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash, cash equivalents and short-term investments to finance our activities. However, we may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt, or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

Critical Accounting Estimates

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

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

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

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

Milestone Payments

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

- Whether the milestone payment is probable (discussed in detail above under ‘‘Determining the transaction price, including any variable consideration’’); and

- Whether the milestone payment relates to services we are performing or if our partner is performing the services:

- If we are performing services, we recognize revenue over our estimated period of performance in a similar manner to the amortization of upfront payments (discussed above under ‘‘R&D Services with Upfront Payments’’).

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

License Fees

When we grant a license for a medicine in clinical development, we generally recognize as R&D revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner. Refer to Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, for our revenue recognition policy. We discuss the estimates we make related to the relative stand-alone selling price of a license in detail above under ''Allocating the transaction price to each of our performance obligations.''

Estimated Liability for Clinical Development Costs

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

As of December 31, 2022, 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 $11.6 million.

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, 2022 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, 2022.

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, 2022, 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, 2022.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2022, 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, 2022, 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, 2022, 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, 2022 and 2021, 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, 2022, and the related notes and our report dated February 22, 2023 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 22, 2023

Item 9B. Other Information

Not applicable.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee from the information under the caption ''ELECTION OF DIRECTORS,'' including in particular the information under ''Nominating, Governance and Review Committee'' and ''Audit Committee,'' contained in our definitive Proxy Statement, which we will file with the Securities and Exchange Commission within 120 days after the end of the fiscal year ended December 31, 2022, or the Proxy Statement.

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

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

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, 2022.

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)]	14,970,226	$50.57	8,158,690[(b)]
Total	14,970,266	$50.57	8,158,690

(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, 492,176 were available for purchase under the ESPP as of December 31, 2022.

For additional details about our equity compensation plans, including a description of each plan, refer to Part IV, Item 15, Note 5, *Stockholders' Equity*, in the Notes to the Consolidated Financial Statements.

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

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

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

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	Indenture, dated as of April 12, 2021, by and between the Registrant and U.S. Bank National Association, as trustee, including Form of 0 percent Convertible Senior Note due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.
4.6	Form of Exchange and/or Subscription Agreement for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.7	Form of Convertible Note Hedge Transactions Confirmation for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.8	Form of Convertible Note Hedge Confirmation for Convertible Senior Notes due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.

Exhibit Number	Description of Document
4.9	Form of Warrant Transactions Confirmation for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.10	Form of Warrant Confirmation for Convertible Senior Notes due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.
10.1	Amended Non-Employee Director Compensation Policy, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2021 and incorporated herein by reference.
10.2*	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 Officers with related schedule, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference.
10.4	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 10b5-1 Trading Plan dated September 12, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference.
10.6*	Registrant's 1989 Stock Option Plan, as amended, filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2012 Annual Meeting of Stockholders, filed on April 16, 2012 and incorporated herein by reference.
10.7*	Form of Option Agreement under the 1989 Stock Option Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference.
10.8*	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.
10.9*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, as amended, filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement for the 2020 Annual Meeting of Stockholders, filed on April 24, 2020 and incorporated herein by reference.
10.10*	Form of Option Agreement for Options granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan.
10.11*	Form of Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on August 7, 2020 and incorporated herein by reference.
10.12*	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.
10.13*	Form of Option Agreement under the 2011 Equity Incentive Plan.
10.14*	Form of Time-Vested Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan.
10.15*	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.
10.16*	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.

Exhibit Number	Description of Document
10.17*	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*	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.
10.19*	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.
10.20*	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.
10.21	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.
10.22	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.
10.23	Lease Agreement between the Registrant and Sudberry Development, Inc. dated October 6, 2022. 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	Purchase and Sale Agreement between Ionis Gazelle, LLC and 2850 2855 & 2859 Gazelle Owner (DE) LLC dated as of October 20, 2022. 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	Purchase and Sale Agreement between the Registrant and Oxford I Asset Management USA Inc. dated as of October 20, 2022. 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.
10.26	Lease Agreement dated October 20, 2022 between the Registrant and 2850 2855 & 2859 Gazelle Owner (DE) LLC. 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.
10.27	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. 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.
10.28	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.
10.29	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. 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.
10.30	Strategic Advisory Services Agreement by and between the Registrant and Stanley T. Crooke, dated December 17, 2020, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2020 and incorporated herein by reference.

Exhibit Number	Description of Document
10.31	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.
10.32	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.
10.33	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.
10.34	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.
10.35	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.
10.36	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.
10.37	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.
10.38	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.
10.39	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.
10.40	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.

Exhibit Number	Description of Document
10.41	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.
10.42	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.
10.43	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.
10.44	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.
10.45	DMPK Research, Development, Option and License Agreement between the Registrant and Biogen Idec MA Inc. dated June 27, 2012, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.46	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.
10.47	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.
10.48	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.
10.49	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.
10.50	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.
10.51	HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

Exhibit Number	Description of Document
10.52	Amendment #1 to HTT Research, Development, Option and License Agreement between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. dated January 9, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.53	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.
10.54	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.
10.55	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.
10.56	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.
10.57	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.
10.58	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.
10.59	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.
10.60	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.
10.61	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.
10.62	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.
10.63	Development, Commercialization, Collaboration, and License Agreement by and between the Registrant and Akcea Therapeutics, Inc., dated March 14, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.

Exhibit Number	Description of Document
10.64	Amended and Restated Services Agreement by and between the Registrant and Akcea Therapeutics, Inc., dated March 14, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2018 and incorporated herein by reference.
10.65	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.
10.66	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.
10.67	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.
10.68	Stock Purchase Agreement by and between the Registrant and Biogen MA Inc., dated April 19, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 and incorporated herein by reference.
10.69	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.
10.70	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.
10.71	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.
10.72	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.
10.73	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.
10.74	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.

Exhibit Number	Description of Document
10.75	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.
10.76	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.
10.77	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.
10.78	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.
10.79	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.
10.80	Collaboration and License Agreement between the Registrant and Metagenomi, Inc. dated November 10, 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.
10.81	Royalty Purchase Agreement by and between the Registrant, Akcea Therapeutics, Inc. and Royalty Pharma Investments 2019 ICAV dated as of January 9, 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.
14	Code of Ethics.
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney – Included on the signature page of this Annual Report on Form 10-K.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1+	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2022, 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 22nd day of February, 2023.

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 22, 2023
/s/ ELIZABETH L. HOUGEN Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer (Principal financial and accounting officer)	February 22, 2023
/s/ JOSEPH LOSCALZO Joseph Loscalzo, M.D., Ph.D.	Chairman of the Board	February 22, 2023
/s/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	February 22, 2023
/s/ ALLENE M. DIAZ Allene M. Diaz	Director	February 22, 2023
/s/ MICHAEL HAYDEN Michael Hayden, CM OBC MB ChB PhD FRCP(C) FRSC	Director	February 22, 2023
/s/ JOAN E. HERMAN Joan E. Herman	Director	February 22, 2023
/s/ JOSEPH KLEIN Joseph Klein, III	Director	February 22, 2023
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director and Senior Strategic Advisor	February 22, 2023
/s/ JOSEPH H. WENDER Joseph H. Wender	Lead Independent Director	February 22, 2023

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, 2022 and 2021, 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, 2022, 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, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, 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, 2022, 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 22, 2023 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 Matter

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

Estimated Liability for Clinical Development Costs

Description of the Matter	As of December 31, 2022, the Company accrued $116.5 million for accrued clinical development costs. As discussed in Note 1 to the consolidated financial statements, the Company estimates their liability for clinical development costs incurred and services received but not yet billed for, and maintains an accrual to cover these costs. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, and investigator grants. The Company estimates their liability using assumptions about study and patient activities and the related expected expenses for those activities determined based on the contracted fees with service providers.

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

How We Addressed the Matter in Our Audit

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

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

/s/ Ernst & Young LLP

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

San Diego, California
February 22, 2023

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

	December 31, 2022	December 31, 2021
ASSETS		
Current assets:		
Cash and cash equivalents	$ 276,472	$ 869,191
Short-term investments	1,710,397	1,245,782
Contracts receivable	25,538	61,896
Inventories	22,033	24,806
Other current assets	168,254	143,374
Total current assets	2,202,694	2,345,049
Property, plant and equipment, net	74,294	178,069
Right-of-use assets	181,544	17,974
Deposits and other assets	75,344	70,598
Total assets	$ 2,533,876	$ 2,611,690
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 17,921	$ 11,904
Accrued compensation	49,178	38,810
Accrued liabilities	140,101	88,560
Income taxes payable	6,249	36
Current portion of deferred contract revenue	90,577	97,714
Other current liabilities	7,535	3,526
Total current liabilities	311,561	240,550
Long-term deferred contract revenue	287,768	351,879
0 percent convertible senior notes, net	622,242	619,119
0.125 percent convertible senior notes, net	544,504	542,314
Long-term lease liabilities	178,941	19,432
Long-term mortgage debt	8,847	59,713
Long-term obligations	7,126	6,946
Total liabilities	1,960,989	1,839,953
Stockholders' equity:		
Common stock, $0.001 par value; 300,000,000 shares authorized, 142,057,736 and 141,210,015 shares issued and outstanding at December 31, 2022 and December 31, 2021, respectively	142	141
Additional paid-in capital	2,059,850	1,964,167
Accumulated other comprehensive loss	(57,480)	(32,668)
Accumulated deficit	(1,429,625)	(1,159,903)
Total stockholders' equity	572,887	771,737
Total liabilities and stockholders' equity	$ 2,533,876	$ 2,611,690

See accompanying notes.

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

	Year Ended December 31,		
	2022	**2021**	**2020**
Revenue:			
Commercial revenue:			
SPINRAZA royalties	$ 242,314	$267,776	$ 286,583
TEGSEDI and WAYLIVRA revenue, net	30,051	55,500	69,999
Licensing and other royalty revenue	30,993	19,119	8,117
Total commercial revenue	303,358	342,395	364,699
Research and development revenue:			
Collaborative agreement revenue	207,222	468,061	364,565
Eplontersen joint development revenue	76,787	—	—
Total research and development revenue	284,009	468,061	364,565
Total revenue	587,367	810,456	729,264
Expenses:			
Cost of sales	14,116	10,842	11,947
Research, development and patent	833,147	643,453	535,077
Selling, general and administrative	150,295	186,347	354,322
Total operating expenses	997,558	840,642	901,346
Loss from operations	(410,191)	(30,186)	(172,082)
Other income (expense):			
Investment income	25,331	10,044	30,562
Interest expense	(8,122)	(9,349)	(9,510)
Gain (loss) on investments	(7,333)	10,103	16,540
Gain on sale of real estate assets	149,604	—	—
Other expenses	(7,274)	(9,760)	(62)
Loss before income tax benefit (expense)	(257,985)	(29,148)	(134,552)
Income tax benefit (expense)	(11,737)	551	(345,191)
Net loss	(269,722)	(28,597)	(479,743)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	—	—	35,480
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$(269,722)	$ (28,597)	$(444,263)
Basic and diluted net loss per share	$ (1.90)	$ (0.20)	$ (3.18)
Shares used in computing basic and diluted net loss per share	141,848	141,021	139,612

See accompanying notes.

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

	Year Ended December 31,		
	2022	2021	2020
Net loss	$(269,722)	$(28,597)	$(479,743)
Unrealized gains (losses) on investments, net of tax	(24,395)	(11,486)	3,729
Currency translation adjustment	(417)	(111)	617
Adjustments to other comprehensive loss from purchase of noncontrolling interest of Akcea Therapeutics, Inc.	—	—	(127)
Comprehensive loss	(294,534)	(40,194)	(475,524)
Comprehensive loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(35,480)
Comprehensive loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	$(294,534)	$(40,194)	$(440,044)

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	Noncontrolling Interest in Akcea Therapeutics, Inc.	Total Stockholders' Equity
Balance at December 31, 2019	140,340	$140	$1,985,650	$(25,290)	$ (596,495)	$1,364,005	$ 213,454	$1,577,459
Net loss	—	—	—	—	(444,263)	(444,263)	—	(444,263)
Change in unrealized gains, net of tax	—	—	—	3,729	—	3,729	—	3,729
Foreign currency translation	—	—	—	617	—	617	—	617
Issuance of common stock in connection with employee stock plans	1,721	1	52,033	—	—	52,034	—	52,034
Purchase of noncontrolling interest of Akcea Therapeutics, Inc., including cash payments for cancellation of Akcea Therapeutics, Inc. equity awards	—	—	(324,022)	301	—	(323,721)	(220,965)	(544,686)
Repurchases and retirements of common stock	(1,478)	(1)	—	—	(90,548)	(90,549)	—	(90,549)
Stock-based compensation expense	—	—	230,117	—	—	230,117	—	230,117
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(217)	—	(13,410)	—	—	(13,410)	—	(13,410)
Deferred tax liability adjustment due to purchase of noncontrolling interest of Akcea Therapeutics, Inc.	—	—	7,714	—	—	7,714	—	7,714
Noncontrolling interest in Akcea Therapeutics, Inc.	—	—	(42,563)	(428)	—	(42,991)	7,511	(35,480)
Balance at December 31, 2020	140,366	$140	$1,895,519	$(21,071)	$(1,131,306)	$ 743,282	$ —	$ 743,282
Net loss	—	—	—	—	(28,597)	(28,597)	—	(28,597)
Change in unrealized losses, net of tax	—	—	—	(11,486)	—	(11,486)	—	(11,486)
Foreign currency translation	—	—	—	(111)	—	(111)	—	(111)
Issuance of common stock in connection with employee stock plans	1,132	1	11,563	—	—	11,564	—	11,564
Issuance of warrants	—	—	89,752	—	—	89,752	—	89,752
Purchase of note hedges	—	—	(136,620)	—	—	(136,620)	—	(136,620)
Stock-based compensation expense	—	—	120,678	—	—	120,678	—	120,678
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(288)	—	(16,725)	—	—	(16,725)	—	(16,725)
Balance at December 31, 2021	141,210	$141	$1,964,167	$(32,668)	$(1,159,903)	$ 771,737	$ —	$ 771,737
Net loss	—	—	—	—	(269,722)	(269,722)	—	(269,722)
Change in unrealized losses, net of tax	—	—	—	(24,395)	—	(24,395)	—	(24,395)
Foreign currency translation	—	—	—	(417)	—	(417)	—	(417)
Issuance of common stock in connection with employee stock plans	1,194	1	6,372	—	—	6,373	—	6,373
Stock-based compensation expense	—	—	100,264	—	—	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)	—	(10,953)
Balance at December 31, 2022	142,058	$142	$2,059,850	$(57,480)	$(1,429,625)	$ 572,887	$ —	$ 572,887

See accompanying notes.

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

	Year Ended December 31,		
	2022	2021	2020
Operating activities:			
Net loss	$ (269,722)	$ (28,597)	$ (479,743)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	14,328	15,487	13,365
Amortization of right-of-use operating lease assets	5,362	1,721	1,731
Amortization of other assets	2,415	2,352	2,064
Amortization of premium on investments, net	7,389	17,776	11,521
Amortization of debt issuance costs	5,373	4,958	3,255
Stock-based compensation expense	100,264	120,678	230,117
Loss on early retirement of debt	—	8,627	—
Non-cash losses related to disposal of property, plant and equipment	531	—	—
Gain on sale of real estate assets	(150,135)	—	—
Gain on investments	224	(1,092)	(16,540)
Deferred income taxes, including changes in valuation allowance	—	—	341,729
Non-cash losses related to other assets	2,030	2,707	1,948
Changes in operating assets and liabilities:			
Contracts receivable	36,358	14,308	(13,170)
Inventories	2,773	(2,841)	(1,261)
Other current and long-term assets	(24,682)	(877)	(9,975)
Long-term income taxes receivable (payable)	—	1,008	(89)
Accounts payable	1,094	(6,000)	(2,755)
Income taxes	6,213	(1,288)	(31,190)
Accrued compensation	10,368	(26,918)	28,371
Accrued liabilities and other current liabilities	46,695	(8,381)	32,424
Deferred contract revenue	(71,248)	(82,829)	(75,910)
Net cash provided by (used in) operating activities	(274,370)	30,799	35,892
Investing activities:			
Purchases of short-term investments	(1,485,772)	(1,124,193)	(1,570,410)
Proceeds from sale of short-term investments	989,152	1,344,185	1,885,935
Purchases of property, plant and equipment	(15,721)	(11,955)	(35,120)
Proceeds from sale of real estate assets	254,083	—	—
Acquisition of licenses and other assets, net	(4,378)	(5,946)	(5,928)
Purchases of strategic investments	—	(7,185)	—
Net cash provided by (used in) investing activities	(262,636)	194,906	274,477
Financing activities:			
Proceeds from equity, net	6,373	11,565	52,036
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(10,953)	(16,725)	(13,411)
Proceeds from the issuance of 0 percent convertible senior notes	—	632,500	—
Royalty monetization issuance costs	(29)	—	—
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)	—

See accompanying notes.

	Year Ended December 31,		
	2022	2021	2020
Proceeds from issuance of warrants	—	89,752	—
Purchase of note hedges	—	(136,620)	—
Repurchases and retirements of common stock	—	—	(90,548)
Principal payments on debt	(50,686)	—	—
Purchase of noncontrolling interest of Akcea Therapeutics, Inc., including cash payments for cancellation of Akcea Therapeutics, Inc. equity awards	—	—	(544,686)
Net cash provided by (used in) financing activities	(55,295)	245,933	(596,609)
Effects of exchange rates on cash	(418)	(111)	617
Net increase (decrease) in cash and cash equivalents	(592,719)	471,527	(285,623)
Cash and cash equivalents at beginning of year	869,191	397,664	683,287
Cash and cash equivalents at end of year	$ 276,472	$ 869,191	$ 397,664
Supplemental disclosures of cash flow information:			
Interest paid	$ 2,898	$ 4,778	$ 6,247
Income taxes paid	$ 5,010	$ 38	$ 25,855
Supplemental disclosures of non-cash investing and financing activities:			
Right-of-use assets obtained in exchange for lease liabilities	$ 168,931	$ 6,641	$ 2,149
Amounts accrued for capital and patent expenditures	$ 4,767	$ 705	$ 4,059

See accompanying notes.

1. Organization and Significant Accounting Policies

Basis of Presentation

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

Organization and Business Activity

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

Use of Estimates

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

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 eplontersen collaboration with AstraZeneca, we recognize funding received from AstraZeneca for co-development activities as revenue; while we recognize cost sharing payments to and from AstraZeneca associated with co-commercialization activities and co-medical affairs activities as SG&A expense and research and development expense, respectively.

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

In some cases, we deliver a license at the start of an agreement. If we determine that our partner has full use of the license and we do not have any additional material performance obligations related to the license after delivery, then we consider the license to be a separate performance obligation. Refer to the section titled, *Eplontersen Collaboration with AstraZeneca*, below for further discussion of a collaboration that included an upfront license payment.

3. Determine the transaction price

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

Milestone payments are our most common type of variable consideration. We recognize milestone payments using the most likely amount method because we will either receive the milestone payment or we will not, which makes the potential milestone payment a binary event. The most likely amount method requires us to determine the likelihood of earning the milestone payment. We include a milestone payment in the transaction price once it is probable we will achieve the milestone event. Most often, we do not consider our milestone payments probable until we or our partner achieve the milestone event because the majority of our milestone payments are contingent upon events that are not within our control and/ or are usually based on scientific progress which is inherently uncertain.

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 research and development, or 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.

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 Part IV, Item 15, Note 7, *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.

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

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

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

Under our collaboration agreement with PTC Therapeutics International Limited, or PTC, PTC is responsible for commercializing TEGSEDI and WAYLIVRA in Latin America and Caribbean countries. Under our agreement, we started receiving royalties from PTC for TEGSEDI sales in December 2021.

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

Under our distribution agreements with Sobi we concluded that our performance obligation is to provide services to Sobi over the term of the agreement, which includes supplying finished goods inventory to Sobi. 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.

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

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.

We provide details about our collaboration agreements in Note 7, *Collaborative Arrangements and Licensing Agreements*. For each collaboration, we discuss our specific revenue recognition conclusions, including our significant performance obligations under each collaboration.

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

We recognize milestone payments that relate to an ongoing performance obligation over our period of performance. For example, 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 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 generally recognize as revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner. This is because our partner has full use of the license and we do not have any additional performance obligations related to the license after delivery.

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.

Eplontersen Collaboration with AstraZeneca

In December 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize eplontersen for the treatment of transthyretin amyloidosis, or ATTR. We are jointly developing and preparing to commercialize eplontersen with AstraZeneca in the U.S. We granted AstraZeneca

exclusive rights to commercialize eplontersen outside the U.S., except certain countries in Latin America. Under the terms of the agreement, we received a $200 million upfront payment in 2021.

We evaluated our eplontersen collaboration under ASC 808 and identified four material components: (i) the license we granted to AstraZeneca in 2021, (ii) the co-development activities that we and AstraZeneca 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 eplontersen 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.

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, 2022, approximately 82.5 percent of our contracts receivables were from one significant customer. As of December 31, 2021, approximately 93.8 percent of our contracts receivables were from two significant customers.

Unbilled SPINRAZA Royalties

Our unbilled SPINRAZA royalties represent our right to receive consideration from Biogen in advance of when we are eligible to bill Biogen for SPINRAZA royalties. We include these unbilled amounts in other current assets 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, 2022 and 2021, we recognized $73.5 million and $98.1 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 research and development operations. We expense research and development costs as we incur them. When we make payments

for research and development services prior to the services being rendered, we record those amounts as prepaid assets in our consolidated balance sheets and we expense them as the services are provided. A portion of the costs included in research and development expenses are costs associated with our partner agreements. In 2022, 2021 and 2020, patent expenses were $4.7 million, $5.3 million and $4.1 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.

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

Basic and Diluted Net Loss per Share

Basic net loss per share

We compute basic net loss per share by dividing the total net loss attributable to our common stockholders by our weighted-average number of common shares outstanding during the period. For the years ended December 31, 2022 and 2021, we did not have to consider Akcea results separately in our calculation because we owned 100 percent of Akcea for the entire period. Our basic net loss per share for the years ended December 31, 2022 and 2021 was $1.90 and $0.20, respectively.

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

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

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

Diluted net loss per share

For the years ended December 31, 2022, 2021 and 2020, we incurred a net loss; therefore, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive. Common stock underlying the following would have had an anti-dilutive effect on net loss per share:

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

For the years ended December 31, 2022 and 2021, common stock underlying the following would also have had an anti-dilutive effect on net loss per share:

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

Additionally as of December 31, 2022 and 2021, we had warrants related to our 0 percent and 0.125 percent Notes outstanding. We will include the shares issuable under these warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

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 year ended December 31, 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 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 grants, one third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (i.e., the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on our relative total shareholder return, or TSR, as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. Under the terms of the grants no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150 percent of the target number depending on our relative TSR.

We determined the fair value of 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 Part IV, Item 15, Note 5, *Stockholders' Equity,* for additional information regarding our stock-based compensation plans.

Noncontrolling Interest in Akcea Therapeutics, Inc.

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

Accumulated Other Comprehensive Loss

Accumulated other comprehensive loss is comprised of unrealized gains and losses on investments, net of taxes and currency translation adjustments. The following table summarizes changes in accumulated other comprehensive loss for the years ended December 31, 2022, 2021 and 2020 (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Beginning balance accumulated other comprehensive loss	$(32,668)	$(21,071)	$(25,290)
Unrealized gains (losses) on securities, net of tax[1]	(24,395)	(11,486)	3,729
Currency translation adjustment	(417)	(111)	617
Adjustments to other comprehensive loss from purchase of noncontrolling interest of Akcea Therapeutics, Inc.	—	—	(127)
Net other comprehensive income (losses) for the year	(24,812)	(11,597)	4,219
Ending balance accumulated other comprehensive loss	$(57,480)	$(32,668)	$(21,071)

(1) We did not have tax expense included in our other comprehensive loss for the years ended December 31, 2022, 2021 and 2020.

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.

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 publicly and privately held biotechnology companies that we received as part of a technology license or partner agreement. At December 31, 2022, we held equity investments in three publicly traded companies and eight 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 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.

Our inventory consisted of the following (in thousands):

	December 31,	
	2022	2021
Raw materials:		
Raw materials- clinical	$17,061	$14,507
Raw materials- commercial	2,699	4,139
Total raw materials	19,760	18,646
Work in process	2,109	5,770
Finished goods	164	390
Total inventory	$22,033	$24,806

Property, Plant and Equipment

We carry our property, plant and equipment at cost and depreciate it on the straight-line method over its estimated useful life, which consists of the following (in thousands):

	Estimated Useful Lives (in years)	December 31,	
		2022	2021
Computer software, laboratory, manufacturing and other equipment	3 to 10	$ 74,351	$ 72,802
Building, building improvements and building systems	15 to 40	41,158	144,046
Land improvements	20	—	10,077
Leasehold improvements	5 to 15	28,357	20,144
Furniture and fixtures	5 to 10	9,575	10,591
		153,441	257,660
Less accumulated depreciation		(87,716)	(102,653)
		65,725	155,007
Land		8,569	23,062
Total		$ 74,294	$ 178,069

In October 2022, we sold the facilities and related land at our headquarters for net proceeds of $202.6 million in connection with a sale and leaseback transaction. In connection with the sale of these real estate assets, 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 (expense) in our consolidated statements of operations.

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

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

	December 31,	
	2022	2021
Clinical expenses	$116,460	$65,730
In-licensing expenses	7,945	8,044
Commercial expenses	3,498	2,471
Other miscellaneous expenses	12,198	12,315
Total accrued liabilities	$140,101	$88,560

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.

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, 2022, we had two outstanding convertible senior notes, our 0% Notes, which mature in April 2026, and our 0.125% Notes, which mature in December 2024. Refer to Part IV, Item 15, Note 4, *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.

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

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

Recently Adopted Accounting Standards

In June 2022, the Financial Accounting Standards Board, or FASB, issued clarifying guidance on fair value measurement of equity securities subject to contractual trading restrictions. The guidance clarifies that contractual trading restrictions are not considered part of the unit of account of equity securities and therefore, are not considered when measuring the fair value of equity securities. This update is effective for interim and annual periods beginning January 1, 2024 on a prospective basis. Early adoption of this guidance is permitted at an interim or annual period. We early adopted this new guidance in the third quarter of 2022. This guidance did not have a material impact on our consolidated financial statements.

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

2. Investments

The following table summarizes the contract maturity of the available-for-sale securities we held as of December 31, 2022:

One year or less	70%
After one year but within two years	28%
After two years but within three and a half years	2%
Total	100%

As illustrated above, at December 31, 2022, 98 percent of our available-for-sale securities had a maturity of less than two years.

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

At December 31, 2022, we had an ownership interest of less than 20 percent in eight privately held companies and three publicly held companies with which we conduct business.

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

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:				
Total equity securities included in other current assets[2]	$ 11,897	$ —	$ (1,358)	$ 10,539
Total 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

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

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

(2) Our equity securities included in other current assets consisted of our investments in publicly traded companies. We recognize publicly traded equity securities at fair value. In the year ended December 31, 2022, we recognized a $7.7 million unrealized non-cash loss in our consolidated statements of operations related to a decrease in the fair value of our investments in publicly traded companies.

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

The following is a summary of our investments we considered to be temporarily impaired at December 31, 2022 (in thousands). All of these investments have less than 12 months of temporary impairment. We believe that the decline in value of these securities is temporary and is primarily related to the change in market interest rates since purchase. We believe it is more likely than not that we will be able to hold our debt securities to maturity. Therefore, we anticipate full recovery of our debt securities' amortized cost basis at maturity.

		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	384	$ 384,136	$(2,629)	$305,367	$(11,879)	$ 689,503	$(14,508)
Debt securities issued by U.S. government agencies	48	93,862	(538)	70,233	(2,331)	164,095	(2,869)
Debt securities issued by the U.S. Treasury	75	616,826	(6,082)	86,325	(3,151)	703,151	(9,233)
Debt securities issued by states of the U.S. and political subdivisions of the states	110	18,117	(225)	31,465	(790)	49,582	(1,015)
Other municipal debt securities	2	—	—	5,993	(14)	5,993	(14)
Total temporarily impaired securities	619	$1,112,941	$(9,474)	$499,383	$(18,165)	$1,612,324	$(27,639)

3. Fair Value Measurements

We use a three-tier fair value hierarchy to prioritize the inputs used in our fair value measurements. These tiers include: Level 1, defined as observable inputs such as quoted prices in active markets for identical assets, which includes our money market funds and treasury securities classified as available-for-sale securities and our investment in equity securities in publicly 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.

The following tables present the major security types we held at December 31, 2022 and 2021 that we regularly measure and carry at fair value. As of December 31, 2022, we did not have any investments that we valued using Level 3 inputs. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

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

	At December 31, 2021	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents[1]	$ 541,199	$541,199	$ —	$ —
Corporate debt securities[2]	764,059	—	764,059	—
Debt securities issued by U.S. government agencies[2]	120,868	—	120,868	—
Debt securities issued by the U.S. Treasury[2]	182,634	182,634	—	—
Debt securities issued by states of the U.S. and political subdivisions of the states[5]	174,464	—	174,464	—
Other municipal debt securities[2]	6,099	—	6,099	—
Publicly traded equity securities included in other current assets[4]	18,205	3,875	—	14,330
Total	$1,807,528	$727,708	$1,065,490	$14,330

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

(2) Included in short-term investments.

(3) $11.0 million included in cash and cash equivalents in our consolidated balance sheets, with the difference included in short-term investments in our consolidated balance sheets.

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

(5) $2.3 million included in cash and cash equivalents in our consolidated balance sheets, with the difference included in short-term investments in our consolidated balance sheets.

Convertible Notes

Our 0.125% Notes and 0% Notes had a fair value of $498.9 million and $587.3 million at December 31, 2022, 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.

4. Long-Term Obligations and Commitments

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

	December 31,	
	2022	2021
0 percent convertible senior notes	$ 622,242	$ 619,119
0.125 percent convertible senior notes	544,504	542,314
Lease liabilities	186,156	22,058
Mortgage debt	8,998	60,054
Other obligations	7,295	7,505
Total	$1,369,195	$1,251,050
Less: current portion	(7,535)	(3,526)
Total Long-Term Obligations	$1,361,660	$1,247,524

Convertible Debt and Call Spread

0 Percent Convertible Senior Notes and Call Spread

In April 2021, we completed a $632.5 million offering of convertible senior notes. We used a portion of the net proceeds from the issuance of the 0% Notes to repurchase $247.9 million in principal of our 1% Notes for $257.0 million.

At December 31, 2022, 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	$10.3
Maturity date	April 2026
Interest rate	0 percent
Effective interest rate	0.5 percent
Conversion price per share	$57.84
Effective conversion price per share with call spread	$76.39
Total shares of common stock subject to conversion	10.9

In conjunction with the April 2021 offering, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0% Notes by increasing the effective conversion price on our 0% Notes. We increased our effective conversion price to $76.39 with the same number of underlying shares as our 0% Notes. The call spread cost us $46.9 million, of which $136.7 million was for the note hedge purchase, offset by $89.8 million we received for selling the warrants. Similar to our 0% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0% Notes. The note hedges will expire upon maturity of the 0% Notes, or April 2026. The note hedges and warrants are separate transactions and are not part of the terms of our 0% Notes. The holders of the 0% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our consolidated balance sheets. Refer to Part IV, Item 15, 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 Percent Convertible Senior Notes and Call Spread

In December 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes.

At December 31, 2022, 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	$548.8
Unamortized debt issuance costs	$4.3
Maturity date	December 2024
Interest rate	0.125 percent
Effective interest rate	0.5 percent
Conversion price per share	$83.28
Effective conversion price per share with call spread	$123.38
Total shares of common stock subject to conversion	6.6

In conjunction with the issuance of our 0.125% Notes in December 2019, we entered into a call spread transaction, which was comprised of purchasing note hedges and selling warrants, to minimize the impact of potential economic dilution upon conversion of our 0.125% Notes by increasing the effective conversion price on our 0.125% Notes. We increased our effective conversion price to $123.38 with the same number of underlying shares as our 0.125% Notes. The call spread cost us $52.6 million, of which $108.7 million was for the note hedge purchase, offset by $56.1 million we received for selling the warrants. Similar to our 0.125% Notes, our note hedges are subject to adjustment. Additionally, our note hedges are exercisable upon conversion of the 0.125% Notes. The note hedges will expire upon maturity of the 0.125% Notes, or December 2024. The note hedges and warrants are separate transactions and are not part of the terms of our 0.125% Notes. The holders of the 0.125% Notes do not have any rights with respect to the note hedges and warrants.

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our consolidated balance sheets. Refer to Part IV, Item 15, 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.

1 Percent Convertible Senior Notes

In April 2021, we repurchased $247.9 million in aggregate principal amount of our 1% Notes in privately negotiated transactions. As a result of the repurchase, we recognized an $8.6 million loss on early retirement of debt in the second quarter of 2021, reflecting the early retirement of a significant portion of our 1% Notes. The loss on the early retirement of our debt is the difference between the amount paid to retire our 1% Notes and the net carrying balance of the liability at the time that we retired the debt. We paid the remaining principal balance of our 1% Notes with $62.0 million of cash at maturity in November 2021.

Other Terms of Convertible Senior Notes

The 0% and 0.125% Notes are convertible under certain conditions, at the option of the note holders. We can settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the notes prior to maturity, and we do not have to provide a sinking fund for them. Holders of the notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indentures governing the notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus any accrued and unpaid interest. The 1% Notes were subject to similar terms.

Our total interest expense for our outstanding senior convertible notes for the years ended December 31, 2022, 2021 and 2020 included $5.3 million, $4.9 million and $3.2 million, respectively, of non-cash interest expense related to the amortization of debt issuance costs for our convertible notes.

Financing Arrangements

Operating Facilities

In July 2017, we purchased the building that houses our primary R&D facility for $79.4 million and our manufacturing facility for $14.0 million. We financed the purchase of these two facilities with mortgage debt of $60.4 million in total. Our primary R&D facility mortgage 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 October 2022 in conjunction with a sale and leaseback transaction.

In October 2022, we concurrently entered into two purchase and sale agreements with a real estate investor. Under the agreements, we sold and leased back the facilities at our headquarters location in Carlsbad, California and will sell, subject to meeting certain closing conditions, two lots of undeveloped land adjacent to our headquarters. We sold the facilities at our headquarters, which includes our primary R&D facility, for a total purchase price of $263.4 million and we expect to receive total proceeds of $33.0 million upon the close of the sale of the two lots. We used a portion of the sale proceeds to extinguish our outstanding mortgage debt on our primary R&D facility of $51.3 million.

Debt Maturity Schedules

Annual convertible and mortgage debt maturities, including fixed and determinable interest, at December 31, 2022 are as follows (in thousands):

2023	$ 1,281
2024	550,107
2025	595
2026	633,095
2027	447
Thereafter	8,708
Total debt and mortgage maturities	$1,194,233
Less: Current portion included in other current liabilities	(151)
Less: Fixed and determinable interest	(3,526)
Less: Debt issuance costs	(14,831)
Total long-term debt	$1,175,725

Operating Leases

Carlsbad Leases

We lease a facility adjacent to our manufacturing facility that has laboratory and office space that we use to support our manufacturing facility. We lease this space under a non-cancelable operating lease. In May 2020, we exercised our option to extend our lease, extending our lease term from June 2021 to August 2026. We have one remaining option to extend the lease for an additional five-year period.

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

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 October 2022. The initial lease term for our headquarters facilities is 15 years with options to extend the lease for 2 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 sale of our two undeveloped lots, we will enter 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. Once this new facility is completed, our lease will commence.

Oceanside Lease

In October 2022, we entered into a build-to-suit lease agreement to lease a development chemistry and manufacturing facility in Oceanside, California. The lessor will develop and construct a building composed of manufacturing space, office space, research and development space and warehouse 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 20 years and 3 months with options to extend the lease for two additional terms of 10 years each. The lease will commence when the lessor's construction is complete and we are able to begin constructing tenant improvements.

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 January 2022, we entered into a sublease agreement for our office space located in Boston, Massachusetts. The sublease commencement date was in January 2022 when the office space was ready for our tenant's occupancy. We are subleasing this space under a non-cancelable operating sublease with a sublease term ending 83 months

following the sublease commencement date with no option to extend the sublease. Under the sublease agreement we provided a seven-month free rent period, which commenced on January 6, 2022. We will receive lease payments over the sublease term totaling $9.6 million.

We entered into an operating lease agreement for another office space located in Boston, Massachusetts which commenced in November 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 on November 1, 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, 2022
Right-of-use operating lease assets	$181.5
Operating lease liabilities	$186.2
Weighted average remaining lease term	13.8 years
Weighted average discount rate	6.9%

During the years ended December 31, 2022, 2021, and 2020 we paid $4.0 million, $3.3 million and $3.8 million of lease payments, which were included in operating activities in our consolidated statements of cash flows.

As of December 31, 2022, the future payments for our operating lease liabilities are as follows (in thousands):

	Operating Leases
Year ending December 31,	
2023	$ 20,071
2024	20,391
2025	20,640
2026	20,781
2027	20,800
Thereafter	196,911
Total minimum lease payments	299,594
Less: Imputed interest	(113,438)
Less: Current portion (included in other current liabilities)	(7,215)
Total long-term lease liabilities	$ 178,941

Rent expense was $8.3 million, $3.4 million and $3.7 million for the years ended December 31, 2022, 2021 and 2020, 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, our medicine in development for lipoprotein(a), or Lp(a), driven cardiovascular disease. 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 will begin accounting for the royalty monetization agreement in the first quarter of 2023.

5. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15 million shares of ''blank check'' Preferred Stock. As of December 31, 2022, 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, 2022.

Common Stock

At December 31, 2022 and 2021, we had 300 million shares of common stock authorized, of which 142.1 million and 141.2 million were issued and outstanding, respectively. As of December 31, 2022, total common shares reserved for future issuance were 43.2 million.

During the years ended December 31, 2022, 2021 and 2020, we issued 1.2 million, 1.1 million and 1.7 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 $6.4 million, $11.6 million and $52.0 million in 2022, 2021 and 2020, respectively.

Share Repurchase Program

In September 2019, our board of directors approved a share repurchase program of up to $125 million of our common stock. In 2019, we repurchased 535,000 shares for $34.4 million. In the first quarter of 2020, we repurchased an additional 1.5 million shares for $90.5 million.

Stock Plans

1989 Stock Option Plan

In June 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20.0 million shares of common stock to our employees, directors, and consultants. The plan expires in January 2024. The 1989 Plan does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 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, 2022, a total of 12 thousand options were outstanding, of which options to purchase 12 thousand shares were exercisable, and 65 thousand shares were available for future grant under the 1989 Plan.

2011 Equity Incentive Plan

In March 2011, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, and performance cash awards to our employees, directors, and consultants. In June 2015, May 2017 and June 2019, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan, or 2011 Plan, to increase the total number of shares reserved for issuance. We increased the shares available under our 2011 Equity Incentive Plan from 5.5 million to 11.0 million in June 2015, from 11.0 million to 16.0 million in May 2017 and from 16.0 million to 23.0 million in June 2019. In the second quarter of 2021, after receiving approval from our stockholders, we amended our 2011 Plan. The amendment increased the total number of shares of common stock authorized for issuance under the 2011 Plan from 23.0 million to 29.7 million and added a fungible share counting ratio whereby the share reserve will be reduced by 1.7 shares for each share of common stock issued pursuant to a full value award (i.e., RSU or PRSU) and increased by 1.7 shares for each share of common stock returning from a full value award. The plan expires in June 2031. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only stock options, RSU and PRSU awards to our employees, directors and consultants. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. Options granted after December 31, 2021 have a term of ten years. We have granted restricted stock unit awards to our employees under

the 2011 Plan which vest annually over a four-year period. At December 31, 2022, a total of 13.7 million options were outstanding, of which 9.4 million were exercisable, 2.7 million restricted stock unit awards were outstanding, and 5.8 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 October 2020, we assumed the unallocated portion of the available share reserve under the Akcea 2015 Equity Incentive Plan. In December 2020, we amended and restated the Akcea 2015 equity plan, including renaming the plan as the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, or 2020 Plan. The 2020 Plan provided for the issuance of up to 2.6 million shares of our Common Stock to our employees, directors and consultants who were employees of Akcea prior to the Akcea Merger. In the second quarter of 2021, our Compensation Committee approved an amendment to the 2020 Plan. The amendment decreased the total number of shares of common stock authorized for issuance under the 2020 Plan from approximately 2.6 million to 1.6 million. We assumed the 2020 Plan in connection with Ionis' reacquisition of all of the outstanding shares of Akcea Therapeutics, Inc. as part of the Akcea Merger.

The plan expires in December 2025. The 2020 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only stock options and RSU awards to our eligible employees, directors and consultants. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. Options granted after December 31, 2021 have a term of ten years. We have granted restricted stock unit awards to our employees under the 2020 Plan which vest annually over a four-year period. At December 31, 2022, a total of 0.3 million options were outstanding, of which 61 thousand were exercisable, 0.1 million restricted stock unit awards were outstanding, and 1.2 million shares were available for future grant under the 2020 Plan.

Under the 2020 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur.

Corporate Transactions and Change in Control under 2011 and 2020 Plans

In the event of certain significant corporate transactions, our Board of Directors has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 and 2020 Plans:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and

- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, our Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options and restricted stock units to our non-employee directors. The name of the resulting plan is the 2002 Non-Employee Directors' Stock Option Plan, or the 2002 Plan. In June 2015, after receiving approval from our stockholders, we amended our 2002 Plan to increase the total number of shares reserved for issuance from 1.2 million to 2.0 million. In June 2020, after receiving approval from our stockholders, we further amended our 2002 Plan. The amendments included:

- An increase to the total number of shares reserved for issuance under the plan from 2.0 million to 2.8 million shares;
- A reduction to the amount of the automatic awards under the plan;
- A revision to the vesting schedule of new awards granted; and
- An extension of the term of the plan.

Options under this plan expire 10 years from the date of grant. At December 31, 2022, a total of 0.9 million options were outstanding, of which 0.8 million were exercisable, 0.1 million restricted stock unit awards were outstanding, and 0.6 million shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In June 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years until 2019, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 3.2 million shares authorized under the plan as of December 31, 2022. 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 2022, employees purchased and we issued to employees 0.1 million shares under the ESPP at a weighted average price of $28.57 per share. At December 31, 2022, there were 0.5 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, 2022 (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, 2021	14,089	$54.04		
Granted	2,864	$34.78		
Exercised	(123)	$29.35		
Cancelled/forfeited/expired	(1,860)	$53.96		
Outstanding at December 31, 2022	14,970	$50.57	4.01	$12,243
Exercisable at December 31, 2022	10,285	$53.74	2.56	$ 1,651

The weighted-average estimated fair values of options granted were $18.66, $24.35 and $29.43 for the years ended December 31, 2022, 2021 and 2020, respectively. The total intrinsic value of options exercised during the years ended December 31, 2022, 2021 and 2020 were $1.4 million, $2.5 million and $15.5 million, respectively,

which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $3.6 million, $8.5 million and $43.7 million for the years ended December 31, 2022, 2021 and 2020, respectively. For the year ended December 31, 2022, the weighted-average fair value of options exercised was $40.71. As of December 31, 2022, total unrecognized compensation cost related to non-vested stock options was $41.1 million. We expect to recognize this cost over a weighted average period of 1.1 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Restricted Stock Unit Activity

The following table summarizes the RSU activity for the year ended December 31, 2022 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2021	2,618	$58.05
Granted	1,401	$36.14
Vested	(958)	$57.05
Cancelled/forfeited	(295)	$48.61
Non-vested at December 31, 2022	2,766	$48.30

For the years ended December 31, 2022, 2021 and 2020, the weighted-average grant date fair value of RSUs granted was $36.14, $57.02 and $60.57 per RSU, respectively. As of December 31, 2022, total unrecognized compensation cost related to RSUs was $45.8 million. We expect to recognize this cost over a weighted average period of 1.2 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Performance Restricted Stock Unit Activity

The following table summarizes the PRSU activity for the year ended December 31, 2022 (in thousands, except per share data):

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Non-vested at December 31, 2021	59	$79.20
Granted	105	$42.28
Vested	(16)	$75.03
Cancelled/forfeited	(5)	$79.11
Non-vested at December 31, 2022	143	$52.59

For the years ended December 31, 2022, 2021 and 2020, the weighted-average grant date fair value of PRSUs granted was $42.28, $77.17 and $93.09 per PRSU, respectively. As of December 31, 2022, total unrecognized compensation cost related to PRSUs was $2.4 million. We expect to recognize this cost over a weighted average period of 0.9 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, 2022, 2021 and 2020 (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Cost of sales	$ 533	$ 456	$ 1,991
Research, development and patent	73,704	87,522	115,584
Selling, general and administrative	26,027	32,700	112,542
Total	$100,264	$120,678	$230,117

In October 2020, as part of the Akcea Merger, Akcea's outstanding equity awards vested under Akcea's Plan. As a result, in 2020, we recognized all unrecognized stock-based compensation, which totaled $59.3 million, under Akcea's Plan.

Refer to Part IV, Item 15, 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, 2022, 2021 and 2020, we used the following weighted-average assumptions in our Black-Scholes calculations:

Ionis Employee Stock Options:

	Year Ended December 31,		
	2022	2021	2020
Risk-free interest rate	2.1%	0.6%	1.5%
Dividend yield	0.0%	0.0%	0.0%
Volatility	54.5%	54.0%	58.6%
Expected life	6.3 years	4.9 years	4.7 years

Ionis Board of Director Stock Options:

	Year Ended December 31,		
	2022	2021	2020
Risk-free interest rate	2.9%	1.2%	0.5%
Dividend yield	0.0%	0.0%	0.0%
Volatility	56.2%	55.9%	57.6%
Expected life	7.4 years	7.3 years	6.7 years

Ionis ESPP:

	Year Ended December 31,		
	2022	2021	2020
Risk-free interest rate	1.2%	0.1%	0.8%
Dividend yield	0.0%	0.0%	0.0%
Volatility	50.1%	42.4%	47.9%
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 year ended December 31, 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.

6. Income Taxes

Income (loss) before income taxes is comprised of (in thousands):

	Year Ended December 31,		
	2022	2021	2020
United States	$(258,493)	$(29,966)	$(137,222)
Foreign	508	818	2,670
Income (loss) before income taxes	$(257,985)	$(29,148)	$(134,552)

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

	Year Ended December 31,		
	2022	2021	2020
Current:			
Federal	$10,522	$(200)	$ (837)
State	1,129	(690)	3,782
Foreign	86	339	518
Total current income tax expense (benefit)	11,737	(551)	3,463
Deferred:			
Federal	—	—	341,728
State	—	—	—
Total deferred income tax benefit	—	—	341,728
Total income tax expense (benefit)	$11,737	$(551)	$345,191

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

	Year Ended December 31,					
	2022		2021		2020	
Pre-tax income (loss)	$(257,985)		$(29,148)		$(134,552)	
Statutory rate	(54,177)	21.0%	(6,121)	21.0%	(28,256)	21.0%
State income tax net of federal benefit	(13,622)	5.3%	4,278	(14.7)%	(37,705)	28.0%
Foreign	(49)	0.0%	143	(0.5)%	49	0.0%
Net change in valuation allowance	104,951	(40.7)%	2,885	(9.9)%	460,898	(342.5)%
Loss on debt transactions	—	—	262	(0.9)%	—	—
Tax credits	(39,729)	15.4%	(23,198)	79.6%	(18,774)	14.0%
Deferred tax true-up	(20)	0.0%	(24)	0.1%	(206)	0.2%
Tax rate change	(3,091)	1.2%	12,838	(44.0)%	(32,951)	24.5%
Non-deductible compensation	3,023	(1.2)%	5,085	(17.4)%	7,931	(5.9)%
Other non-deductible items	57	0.0%	84	(0.3)%	193	(0.1)%
Stock-based compensation	14,030	(5.4)%	4,720	(16.2)%	17,435	(13.0)%
Impacts from Akcea Merger	—	—	—	—	(22,032)	16.4%
Other	364	(0.1)%	(1,503)	5.1%	(1,391)	0.9%
Effective rate	$ 11,737	(4.5)%	$ (551)	1.9%	$ 345,191	(256.5)%

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, 2022 and 2021 are as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Deferred Tax Assets:		
Net operating loss carryovers	$ 87,802	$ 85,600
Tax credits	277,436	269,538
Deferred revenue	85,700	104,330
Stock-based compensation	86,983	86,611
Intangible and capital assets	104,649	92,542
Convertible debt	34,384	45,681
Interest expense limitation	—	6,996
Capitalized research and development expenses	119,635	—
Long-term lease liabilities	45,612	5,119
Other	15,813	9,929
Total deferred tax assets	$ 858,014	$ 706,346
Deferred Tax Liabilities:		
Fixed assets	(4,475)	(3,303)
Right-of-use assets	(44,504)	(4,159)
Other	(313)	(1,111)
Net deferred tax asset	$ 808,722	$ 697,773
Valuation allowance	(808,722)	(697,773)
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 $111 million from December 31, 2021 to December 31, 2022. The increase was primarily related to increases in our deferred tax asset for capitalized research and development expenses.

At December 31, 2022, we had federal and state, primarily California, tax net operating loss carryforwards of $242.8 million and $461.3 million, respectively. Our federal tax loss carryforwards are available indefinitely. Our California tax loss carryforwards will begin to expire in 2031. At December 31, 2022, we also had federal and California research and development tax credit carryforwards of $224.9 million and $110.7 million, respectively. Our federal research and development tax credit carryforwards will begin to expire in 2035. Our California research and development tax credit carryforwards are available indefinitely.

Utilization of the net operating loss and tax credit carryforwards may be subject to an annual limitation due to the ownership change limitations provided by the Internal Revenue Code of 1986, as amended, and similar state provisions. The annual limitation may result in the expiration of net operating losses and credits before utilization.

We analyze filing positions in all U.S. federal, state and foreign jurisdictions where we file income tax returns, and all open tax years in these jurisdictions to determine if we have any uncertain tax positions on any of our income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize uncertain income tax positions if they have less than 50 percent likelihood of the applicable tax authority sustaining our position.

The following table summarizes our gross unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Beginning balance of unrecognized tax benefits	$55,085	$54,163	$ 69,784
Decrease for prior period tax positions	(267)	(695)	(24,154)
Increase for prior period tax positions	259	263	7,023
Increase for current period tax positions	1,490	1,354	1,510
Ending balance of unrecognized tax benefits	$56,567	$55,085	$ 54,163

Included in the balance of unrecognized tax benefits at December 31, 2022, 2021 and 2020 was $6.2 million, $6.2 million and $6.4 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 $15.0 million within the next 12 months due to the lapse of statute of limitations on underlying tax positions primarily related to tax credits.

We recognize interest and/or penalties related to income tax matters in income tax expense. During the years ended December 31, 2022, 2021 and 2020, we recognized $0.8 million, $0.5 million and $0.3 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. The tax years 2018 through 2021 remain open to examination by major taxing jurisdictions, primarily federal and California, although net operating loss and credit carryforwards generated prior to 2018 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.

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

7. Collaborative Arrangements and Licensing Agreements

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. We and Biogen are currently developing numerous investigational medicines to treat neurodegenerative diseases under these collaborations, including medicines in development to treat people with ALS, SMA, AS, AD and Parkinson's disease. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through December 31, 2022, we have received more than $3.4 billion from our Biogen collaborations.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In January 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA. From inception through December 31, 2022, we earned more than $1.8 billion in total revenue under our SPINRAZA collaboration, including more than $1.4 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 January 2023, we entered into a royalty purchase agreement with Royalty Pharma in which 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. 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, which Novartis is developing. Refer to Part IV, Item 15, Note 4, *Long-Term Obligations and Commitments*, for further discussion of this agreement.

New antisense medicines for the treatment of SMA

In December 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies. Under the collaboration agreement, we received a $25 million upfront payment in the fourth quarter of 2017. In December 2021, we earned a $60 million license fee payment when Biogen exercised its option to license ION306. We will receive development and regulatory milestone payments from Biogen if new medicines, including ION306, advance towards marketing approval.

Over the term of the collaboration, we are eligible to receive up to $1.2 billion, which is comprised of a $25 million upfront payment, up to $110 million in license fees, up to $80 million in development milestone payments, up to $180 million in regulatory milestone payments, up to $800 million in sales milestone payments and other payments, including up to $555 million if Biogen advances ION306, which includes 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 inception through December 31, 2022, 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.

At the commencement of this collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. We determined the transaction price to be the $25 million upfront payment we received when we entered into the collaboration. We allocated the transaction price to our single performance obligation. In the fourth quarter of 2019, we completed our R&D services performance obligation under this collaboration.

In the fourth quarter of 2021, we identified another performance obligation upon Biogen's license of ION306 because the license we granted to Biogen is distinct from our other performance obligations. We recognized the $60 million license fee for ION306 as revenue at that time because Biogen had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Biogen. Biogen is solely responsible for the costs and expenses related to the development, manufacturing and potential future commercialization of ION306 following the option exercise. We do not have any remaining performance obligations under this collaboration.

Neurology Collaborations

2018 Strategic Neurology

In April 2018, we and Biogen entered into a strategic collaboration to develop novel antisense medicines for a broad range of neurological diseases and entered into a 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 medicines. Biogen is responsible for conducting IND-enabling toxicology studies for the selected medicine. Biogen will have the option to license the selected medicine after it completes the IND-enabling toxicology study. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine.

In the second quarter of 2018, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at an approximately 25 percent cash premium and $375 million in an upfront payment.

Over the term of our 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 for each medicine that achieves marketing approval. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales. We are currently advancing multiple programs under this

collaboration and from inception through December 31, 2022, we have received nearly $1.1 billion in payments under this collaboration. We will achieve the next payment of $7.5 million if Biogen designates or advances another program under this collaboration.

At the commencement of 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, 2022, we have included $616 million in payments in the transaction price for our R&D services performance obligation under this collaboration, including $23 million of milestone payments we achieved in 2021 and $11 million of milestone payments we achieved in 2020. These milestone payments did not create new performance obligations because they are part of our original R&D services performance obligation. Therefore, we included these amounts in our transaction price for our R&D services performance obligation in the period we achieved the milestone payment. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation at the end of the contractual term in June 2028.

2013 Strategic Neurology

In September 2013, we and Biogen entered into a long-term strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. We will usually be responsible for drug discovery and early development of antisense medicines and Biogen has the option to license antisense medicines after Phase 2 proof-of-concept. In October 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine. We are currently advancing five investigational medicines in development under this collaboration, including a medicine for Parkinson's disease (ION859), two medicines for ALS (tofersen and ION541), a medicine for multiple system atrophy (ION464) and a medicine for an undisclosed target. In the fourth quarter of 2018, Biogen exercised its option to license our most advanced ALS medicine, tofersen, our medicine in registration for SOD1 ALS. As a result, Biogen is responsible for global development, regulatory and commercialization activities and costs for tofersen.

Under the terms of the agreement, we received an upfront payment of $100 million and are eligible to receive milestone payments, license fees and royalty payments for all medicines developed under this collaboration, with the specific amounts dependent upon the modality of the molecule advanced by Biogen. Under this collaboration, we received a $35 million license fee payment when Biogen licensed tofersen from us in 2018.

Over the term of the collaboration for tofersen, we are eligible to receive nearly $110 million, which is comprised of the $35 million license fee received in 2018, up to $18 million in development milestone payments and up to $55 million in regulatory milestone payments. 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, including amounts related to the cost of clinical trials, 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 antisense medicines developed under this collaboration. From inception through December 31, 2022, we have received more than $300 million in payments under this collaboration. We will achieve the next payment of $16 million if the FDA approves Biogen's NDA filing of tofersen.

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 research and development services and recognized the remaining revenue related to this performance obligation. From inception through the completion of our R&D services performance obligation in 2020, we included $145 million in total payments in the transaction price for our R&D services performance obligation.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter we generated the payment because we did not have any performance obligations for the respective payment. For example, in the third quarter of 2022, we earned a $9 million milestone payment when the FDA accepted Biogen's NDA filing of tofersen, which we recognized in full because we did not have any performance obligations related to this milestone payment.

2012 Neurology

In December 2012, we and Biogen entered into a collaboration agreement to develop and commercialize novel antisense medicines to treat neurodegenerative diseases. We are responsible for the development of each of the medicines through the completion of the initial Phase 2 clinical study for such medicine. Biogen has the option to license a medicine from each of the programs through the completion of the first Phase 2 study for each program. Under this collaboration, 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.

Under the terms of the agreement, we received an upfront payment of $30 million. Over the term of the collaboration, we are eligible to receive up to $210 million, which is comprised of a $70 million license fee, up to $10 million in development milestone payments per program and up to $130 million in regulatory milestone payments per program, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales of any medicines resulting from each of the two programs. From inception through December 31, 2022, we have received nearly $170 million in payments under this collaboration, including nearly $20 million in milestone payments we received from Biogen for advancing ION582 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 up to $25 million if Biogen advances a medicine under this collaboration.

Under our collaboration, we determined we had a performance obligation to perform R&D services. We allocated $40 million in total payments to the transaction price for our R&D services performance obligation. In the third quarter of 2019, we completed our R&D services performance obligation when we designated a development candidate and Biogen accepted the development candidate. We recognized revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation.

When we commenced development for IONIS-MAPT$_{Rx}$ we identified our development work as a separate performance obligation. In the fourth quarter of 2022, we completed our R&D services performance obligation for IONIS-MAPT$_{Rx}$. We recognized revenue as we performed services based on our effort to satisfy our performance obligation relative to the total effort expected to satisfy our performance obligation. From inception through December 31, 2022, 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}$.

In the fourth quarter of 2019, we identified another performance obligation upon Biogen's license of IONIS-MAPT$_{Rx}$ because the license we granted to Biogen is distinct from our other performance obligations. We recognized the $45 million license fee for IONIS-MAPT$_{Rx}$ as revenue at that time because Biogen had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to Biogen. Biogen is responsible for global development, regulatory and commercialization activities and costs for IONIS-MAPT$_{Rx}$.

In the fourth quarter of 2022, we achieved $14.5 million in milestone payments when Biogen advanced ION582. We will recognize revenue as we perform services based on our effort to satisfy our R&D services performance obligation relative to the total effort expected to satisfy our performance obligation for ION582.

During the years ended December 31, 2022, 2021 and 2020, we earned the following revenue from our relationship with Biogen (in millions, except percentage amounts):

	Year Ended December 31,		
	2022	2021	2020
SPINRAZA royalties (commercial revenue)	$242.3	$267.8	$286.6
R&D revenue	124.4	161.0	122.0
Total revenue from our relationship with Biogen	$366.7	$428.8	$408.6
Percentage of total revenue	62%	53%	56%

Our consolidated balance sheets at December 31, 2022 and 2021 included deferred revenue of $351.2 million and $407.5 million, respectively, related to our relationship with Biogen.

Joint Development and Commercialization Arrangement

AstraZeneca

Eplontersen Collaboration

In December 2021, we entered into a joint development and commercialization agreement with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. We are jointly developing and preparing to commercialize eplontersen with AstraZeneca in the U.S. We granted AstraZeneca exclusive rights to commercialize eplontersen outside the U.S., except certain countries in Latin America.

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, up to $485 million in development and approval milestone payments and up to $2.9 billion in sales milestone payments. The agreement also includes territory-specific development, commercial and medical affairs cost-sharing provisions. In addition, we are eligible to receive up to mid-20 percent royalties for sales in the U.S. and tiered royalties up to the high teens for sales outside the U.S.

We evaluated our eplontersen collaboration under ASC 808 and identified four material components: (i) the license we granted to AstraZeneca in 2021, (ii) the co-development activities that we and AstraZeneca will perform, (iii) the co-commercialization activities that we and AstraZeneca will perform and (iv) the co-medical affairs activities that we and AstraZeneca will perform.

We determined that we had a vendor-customer relationship within the scope of ASC 606 for the license we granted to AstraZeneca and as a result we had one performance obligation. For our sole performance obligation, we determined the transaction price was the $200 million upfront payment we received. We recognized the upfront payment in full in 2021 because we did not have any remaining performance obligations after we delivered the license to AstraZeneca.

We also concluded that the co-development activities, the co-commercialization activities and the co-medical affairs activities are within the scope of ASC 808 because we and AstraZeneca are active participants exposed to the risks and benefits of the activities under the collaboration. AstraZeneca 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 eplontersen 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.

We will achieve the next payment of up to $50 million upon the first regulatory approval under this collaboration. From inception through December 31, 2022, we have received nearly $260 million in payments under this collaboration.

Research and Development Partners

AstraZeneca

In addition to our collaboration for eplontersen, we have a collaboration with AstraZeneca focused on the treatment of cardiovascular, renal and metabolic diseases. In July 2015, we and AstraZeneca formed a collaboration to discover and develop antisense therapies for treating cardiovascular, renal and metabolic diseases. Under our

collaboration, AstraZeneca has licensed multiple medicines from us, including medicines in development to treat people with ATTR amyloidosis, a genetically associated form of kidney disease and NASH. 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 $5.8 billion, which is comprised of a $65 million upfront payment, up to $290 million in license fees, up to $1.1 billion in development milestone payments, up to $2.9 billion in regulatory milestone payments and up to $1.5 billion in sales 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. We will achieve the next payment of $10 million under this collaboration if AstraZeneca advances a medicine under this collaboration. From inception through December 31, 2022, we have received more than $280 million in payments 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 the fourth quarter of 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 quarter we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. For example, in the fourth quarter of 2021, we earned a $30 million license fee when AstraZeneca licensed a target for a metabolic disease. We recognized the license fee as revenue at that time because AstraZeneca had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to AstraZeneca.

During the years ended December 31, 2022, 2021 and 2020, we earned the following revenue from our relationship with AstraZeneca (in millions, except percentage amounts):

	Year Ended December 31,		
	2022	2021	2020
R&D revenue	$79.2	$254.6	$88.0
Percentage of total revenue	13%	31%	12%

We did not have any deferred revenue from our relationship with AstraZeneca at December 31, 2022 and 2021.

GSK

In March 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 and some conditions causing blindness. Our collaboration with GSK currently includes two medicines targeting hepatitis B virus, or HBV: bepirovirsen and IONIS-HBV-L_{Rx}. We designed these medicines to reduce the production of viral proteins associated with HBV infection. In the third quarter of 2019, following positive Phase 2 results, GSK licensed our HBV program. GSK is responsible for all global development, regulatory and commercialization activities and costs for the HBV program.

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 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, 2022, we have received more than $50 million in payments under the HBV program collaboration.

We completed our R&D services performance obligations under our collaboration in the first quarter of 2015. We identified a new performance obligation when we granted GSK the license of the HBV program and assigned

related intellectual property rights in the third quarter of 2019 because the license was distinct from our other performance obligations. We recognized the $25 million license fee for the HBV program as revenue at that time because GSK had full use of the license without any continuing involvement from us. Additionally, we did not have any further performance obligations related to the license after we delivered it to GSK.

We do not have any remaining performance obligations under our collaboration with GSK; however, we can still earn additional payments and royalties as GSK advances the HBV program. In January 2023, we earned a $15 million milestone when GSK initiated a Phase 3 study of bepirovirsen. 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, 2022, 2021 and 2020, we earned the following revenue from our relationship with GSK (in millions, except percentage amounts):

	Year Ended December 31,		
	2022	2021	2020
R&D revenue	$—	$—	$0.2
Percentage of total revenue	—	—	—

We did not have any deferred revenue from our relationship with GSK at December 31, 2022 and 2021.

Novartis

In January 2017, we initiated a collaboration with Novartis to develop and commercialize pelacarsen and olezarsen. 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 the fourth quarter 2019. In connection with Novartis' license of pelacarsen, we and Novartis established a more definitive framework under which the companies would negotiate the co-commercialization of pelacarsen in selected markets. Included in this framework is an option by which Novartis could solely commercialize pelacarsen in exchange for Novartis paying us increased sales milestone payments based on sales of pelacarsen. When Novartis decided to not exercise its option for olezarsen, we retained rights to develop and commercialize olezarsen.

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. From inception through December 31, 2022, we have received nearly $275 million in payments under this collaboration. We are also eligible to receive tiered royalties in the mid-teens to low 20 percent range on net sales of pelacarsen. In August 2021, we earned a $25 million milestone payment from Novartis when Novartis achieved 50 percent enrollment in the Lp(a) HORIZON Phase 3 cardiovascular outcome study of pelacarsen. We recognized the milestone payment in full in the third quarter of 2021 because we did not have any remaining performance obligations related to the milestone payment. We will achieve the next payment of up to $75 million if Novartis advances regulatory activities for pelacarsen.

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

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

- R&D services for pelacarsen;
- R&D services for olezarsen;
- API for pelacarsen; and
- API for olezarsen.

We determined that the R&D services for each medicine and the API for each medicine were distinct performance obligations.

We determined our transaction price to be $108.4 million, comprised of the following:

- $75 million from the upfront payment;
- $28.4 million for the premium paid by Novartis for its purchase of our common stock at a premium in the first quarter of 2017; and
- $5.0 million for the potential premium Novartis would have paid if they purchased our common stock in the future.

We allocated the transaction price based on the estimated stand-alone selling price of each performance obligation as follows:

- $64.0 million for the R&D services for pelacarsen;
- $40.1 million for the R&D services for olezarsen;
- $1.5 million for the delivery of pelacarsen API; and
- $2.8 million for the delivery of olezarsen API.

We completed our R&D services performance obligations for olezarsen and pelacarsen in 2019. As such, we recognized all revenue we allocated to the olezarsen and pelacarsen R&D services as of the end of 2019.

We recognized revenue related to the R&D services for pelacarsen and olezarsen performance obligations as we performed services based on our effort to satisfy our performance obligations relative to our total effort expected to satisfy our performance obligations.

During the years ended December 31, 2022, 2021 and 2020, we earned the following revenue from our relationship with Novartis (in millions, except percentage amounts):

	Year Ended December 31,		
	2022	2021	2020
R&D revenue	$0.2	$25.5	$1.0
Percentage of total revenue	—	3%	—

We did not have any deferred revenue from our relationship with Novartis at December 31, 2022 and 2021.

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 Part IV, Item 15, Note 4, *Long-Term Obligations and Commitments*, for further discussion of this agreement.

Roche

Huntington's Disease

In April 2013, we formed an alliance 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 the fourth quarter of 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen. Roche is responsible for all global development, regulatory and commercialization activities and costs for tominersen.

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 alliance. From inception through December 31, 2022, 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 the third quarter of 2017.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective quarter in which we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. In 2019, we earned $35 million in milestone payments when Roche advanced tominersen under this collaboration. In March 2021, Roche decided to discontinue dosing in the Phase 3 GENERATION HD1 study of tominersen in patients with manifest HD based on the results of a pre-planned review of data from the Phase 3 study conducted by an unblinded iDMC.

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 October 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. We are currently conducting Phase 2 studies in two disease indications for IONIS-FB-L_{Rx}, one for the treatment of patients with GA, the advanced stage of dry AMD, and a second for the treatment of patients with IgA nephropathy.

After positive data from a Phase 2 clinical study, Roche licensed IONIS-FB-L_{Rx} in July 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 July 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 milestones, up to $279 million in regulatory milestones 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, 2022, we have received more than $130 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. We determined the transaction price to be the $75 million upfront payment we received and allocated it to our single performance obligation. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation in the third quarter of 2024.

During the years ended December 31, 2022, 2021 and 2020, we earned the following revenue from our relationship with Roche (in millions, except percentage amounts):

	Year Ended December 31,		
	2022	2021	2020
R&D revenue	$67.2	$17.2	$5.9
Percentage of total revenue	11%	2%	1%

Our consolidated balance sheets at December 31, 2022 and 2021 included deferred revenue of $22.4 million and $31.6 million related to our relationship with Roche, respectively.

Commercialization Partnerships

Swedish Orphan Biovitrum AB (Sobi)

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

PTC Therapeutics

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

Technology Enhancement Collaborations

Bicycle License Agreement

In December 2020, we entered into a collaboration agreement with Bicycle and obtained an option to license its peptide technology to potentially increase the delivery capabilities of our LICA medicines. In July 2021, we paid $42 million when we exercised our option to license Bicycle's technology, which included an equity investment in Bicycle. As part of our stock purchase, we entered into a lockup agreement with Bicycle that 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. From inception through December 31, 2022, we have paid Bicycle $46.6 million under this collaboration agreement.

Metagenomi License Agreement

In November 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. 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. We will also pay Metagenomi certain fees for the selection of genetic targets, and contingent on the achievement of certain development, regulatory and sales events, milestone payments and royalties. In addition, we will 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 4 therapeutic programs. Alnylam granted us an exclusive, royalty-bearing license to its chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four targets, including FXI and Apo(a) and two other targets. In exchange, we granted Alnylam an exclusive, royalty-bearing license to our chemistry, RNA targeting mechanism and target-specific intellectual property for oligonucleotides against four other targets. Alnylam also granted us a royalty-bearing, non-exclusive license to new

platform technology arising from May 2014 through April 2019 for single-stranded antisense therapeutics. In turn, we granted Alnylam a royalty-bearing, non-exclusive license to new platform technology arising from May 2014 through April 2019 for double-stranded RNAi therapeutics.

In the fourth quarter 2020, we completed an arbitration process with Alnylam. The arbitration panel awarded us $41.2 million for payments owed to us by Alnylam related to Alnylam's agreement with Sanofi Genzyme. We recognized the $41.2 million payment from Alnylam as revenue in the fourth quarter of 2020 because we did not have any performance obligations for the respective payment.

During the years ended December 31, 2022, 2021 and 2020, we earned the following revenue from our relationship with Alnylam (in millions, except percentage amounts):

	Year Ended December 31,		
	2022	2021	2020
R&D revenue	$21.4	$—	$47.9
Percentage of total revenue	4%	—	7%

We did not have any deferred revenue from our relationship with Alnylam at December 31, 2022 and 2021.

8. Employment Benefits

We have employee 401(k) salary deferral plans covering all employees. Employees could make contributions by withholding a percentage of their salary up to the IRS annual limits of $20,500 and $27,000 in 2022 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $5.6 million, $5.5 million and $5.7 million in matching contributions for the years ended December 31, 2022, 2021 and 2020, respectively.

9. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If 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.

On August 5, 2021, four purported former stockholders of Akcea filed an action in the Delaware Court of Chancery captioned John Makris, et al. v. Ionis Pharmaceuticals, Inc., et al., C.A. No. 2021-0681, or the Delaware Action. The plaintiffs in the Delaware Action asserted claims against (i) former members of Akcea's board of directors; and (ii) Ionis, or collectively, the Defendants. The plaintiffs asserted putatively direct claims on behalf of a purported class of former Akcea stockholders. The plaintiffs in the Delaware Action asserted that the Defendants breached their fiduciary duties in connection with the October 2020 take-private transaction that Ionis and Akcea entered into, in which Akcea became a wholly-owned subsidiary of Ionis. We believe this lawsuit is without merit. However, the outcome of this lawsuit or any other lawsuit that may be filed challenging the October 2020 take-private transaction is uncertain. Accordingly, on June 3, 2022, the parties reached an agreement in principle to settle the Delaware Action for $12.5 million. A Stipulation and Agreement of Compromise, Settlement and Release, or the Stipulation and Settlement Agreement reflecting the terms of the proposed settlement was executed and filed with the Delaware Court of Chancery on July 5, 2022. On October 11, 2022, the Delaware Court of Chancery entered an Order and Final Judgment, or the Order, approving the Stipulation and Settlement Agreement in full after determining that the Stipulation and Settlement Agreement was fair, reasonable, and adequate. The Order provides for the full settlement, satisfaction, compromise and release of all claims that were asserted in the Delaware Action. The Order contains no admission of wrongdoing on the part of any of the Defendants. We recorded a net settlement expense of $7.7 million within other expense in the accompanying consolidated statements of operations in 2022.

On January 19, 2022, a purported stockholder of Ionis filed a stockholder derivative complaint in the Delaware Court of Chancery captioned Leo Shumacher, et al. v. Joseph Loscalzo, et al., C.A. No. 2022-0059, or the Shumacher Action. The complaint names Ionis' board of directors, or the Board, as defendants and names Ionis as a nominal defendant. The Shumacher Action Plaintiff asserts a breach of fiduciary duty claim against the Board for awarding

and receiving allegedly excessive compensation. The Shumacher Action Plaintiff also asserts an unjust enrichment claim against the non-executive directors as a result of the compensation they received. The complaint seeks, among other things, damages, restitution, attorneys' fees and costs, and such other relief as deemed just and proper by the court. On March 18, 2022, Ionis and the Board moved to dismiss the complaint. On May 24, 2022, the parties entered into a Stipulation and Agreement of Compromise, Settlement and Release.

On May 25, 2022, another purported stockholder of Ionis filed a stockholder derivative complaint also in the Delaware Court of Chancery captioned Robert S. Cohen, et al. v. Joseph Loscalzo, et al., C.A. No. 2022-0453, or the Cohen Action. The complaint names the Board as defendants and names Ionis as a nominal defendant. The Cohen Action Plaintiff asserts claims for breach of fiduciary duty, unjust enrichment, aiding and abetting breaches of fiduciary duty, and waste against the Board for awarding and receiving allegedly excessive non-executive director compensation for the years 2018, 2019, and 2020. On June 2, 2022, the Cohen Action Plaintiff filed a motion to consolidate the related Cohen Action and Shumacher Action. On July 5, 2022, the Court denied the motion to consolidate in favor of the settlement pending in the Shumacher Action.

On July 18, 2022, Ionis filed a Form 8-K disclosing the pending settlement and attaching the Notice of Pendency of Settlement of Action. On September 21, 2022, the Court held a hearing to consider whether the terms of the settlement should be approved, at which hearing the Cohen Action plaintiff objected to the settlement. At the conclusion of the hearing, the Court declined to approve the settlement and directed the parties to meet and confer on the issue of the scope of the release. On February 7, 2023, the parties entered into an Amended Stipulation and Agreement of Compromise, Settlement and Release. We and our Board have denied, and continue to deny, any and all allegations of wrongdoing or liability asserted in the Shumacher and Cohen Actions.

10. 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 2022 and 2021 are as follows (in thousands, except per share data).

Three Months Ended December 31,	2022	2021
Revenue[1]	$ 151,890	$440,006
Operating expenses[2]	$ 359,909	$219,403
Income (loss) from operations	$(208,019)	$220,603
Net income (loss)[3]	$ (52,430)	$224,613
Basic net income (loss) per share[4][5]	$ (0.37)	$ 1.59
Diluted net income (loss) per share[4][6]	$ (0.37)	$ 1.41

(1) Revenue was lower in the three months ended December 31, 2022 compared to the same period in 2021 due to the $200 million we earned in the fourth quarter of 2021 from AstraZeneca to jointly develop and commercialize eplontersen.

(2) Operating expenses were higher in the three months ended December 31, 2022 compared to the same period in 2021 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 income (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 income (loss) per share by dividing the total net income (loss) by our weighted-average number of common shares outstanding during the period.

(6) We had net income for the fourth quarter of 2021. As a result, we computed diluted net income per share using the weighted-average number of common shares and dilutive common equivalent shares outstanding during the period as follows (in thousands except per share amounts):

Three Months Ended December 31, 2021	Income (Numerator)	Shares (Denominator)	Per-Share Amount
Net income available to Ionis common stockholders	$224,612	141,205	$1.59
Effect of dilutive securities:			
Shares issuable upon exercise of stock options	—	46	
Shares issuable upon restricted stock award issuance	—	1,065	
Shares issuable related to our ESPP	—	34	
Shares issuable related to our 0 percent convertible notes	777	10,936	
Shares issuable related to our 0.125 percent convertible notes	716	6,590	
Shares issuable related to our 1 percent convertible notes	105	464	
Income available to Ionis common stockholders, plus assumed conversions	$226,210	160,340	$1.41

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