UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-K

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

For the fiscal year ended December 31, 2023

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

For the transition period from _____ to _____

Commission file number 000-19125

Ionis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

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

760-931-9200

(Registrant's telephone number, including area code)

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

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

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

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

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

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

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

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

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

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

Indicate by check mark whether the registrant has filed a report on and attestation to its management assessment of the effectiveness of its internal controls over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered

public accounting firm that prepared or issued its audit report ☒

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

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

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

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on The Nasdaq Global Select Market was $4,243,321,410 as of June 30, 2023.*

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

DOCUMENTS INCORPORATED BY REFERENCE

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

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* Excludes 39,747,443 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10 percent of the common stock outstanding at June 30, 2023. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K and the information incorporated herein by reference includes forward-looking statements regarding our business and the therapeutic and commercial potential of our commercial medicines, additional medicines in development and technologies. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements.

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

Summary of Risk Factors

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

- Our ability to generate substantial revenue from the sale of our medicines;
- The availability of adequate coverage and payment rates for our medicines;
- Our and our partners' ability to compete effectively;
- Our ability to successfully manufacture our medicines;
- Our ability to successfully develop and obtain marketing approvals for our medicines;
- Our ability to secure and maintain effective corporate partnerships;
- Our ability to sustain cash flows and achieve consistent profitability;
- Our ability to protect our intellectual property;
- Our ability to maintain the effectiveness of our personnel; and
- The impacts of pandemics, climate change, wars and other global events.

TRADEMARKS

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

CORPORATE INFORMATION

We incorporated in California in 1989 and in January 1991 we changed our state of incorporation to Delaware. In December 2015, we changed our name to Ionis Pharmaceuticals, Inc. from Isis Pharmaceuticals, Inc. Our principal offices are in Carlsbad, California.

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

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IONIS PHARMACEUTICALS, INC.
FORM 10-K
For the Fiscal Year Ended December 31, 2023
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PART I

Item 1. Business

Overview

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

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

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

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

Marketed Medicines

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

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

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

TEGSEDI is a once weekly, self-administered subcutaneous medicine approved in the U.S., Europe, Canada and Brazil for the treatment of patients with ATTRv-PN. We sell TEGSEDI in the U.S. and Canada (collectively, North America) and Europe through our distribution agreement with Swedish Orphan Biovitrum AB, or Sobi. In October 2023, our agreement for TEGSEDI in North America was terminated. As a result, Sobi is transitioning responsibilities to us. In February 2024, we began the process to withdraw the TEGSEDI New Drug Application, or NDA. In Latin America, PTC Therapeutics International Limited, or PTC, is commercializing TEGSEDI in Brazil and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

WAYLIVRA is a once weekly, self-administered, subcutaneous medicine approved in Europe and Brazil as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome, or FCS, and at high risk for pancreatitis. We sell WAYLIVRA in Europe through our distribution agreement with Sobi. In Latin America, PTC is commercializing WAYLIVRA in Brazil for two indications, FCS and familial partial lipodystrophy, or FPL, and is pursuing access in additional Latin American countries through its exclusive license agreement with us.

Medicines in Registration and Phase 3 Studies

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

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

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

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

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

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

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

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

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

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

Our Marketed Medicines –Bringing Value to Patients Today

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

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

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

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

Biogen continues to expand the body of evidence supporting SPINRAZA's durable efficacy and well-established safety profile to address the remaining needs of SMA patients of all ages. This includes the following ongoing studies:

- DEVOTE: In the Phase 2/3 DEVOTE study, Biogen is evaluating the safety and potential to achieve increased efficacy with a higher dose of SPINRAZA compared to the currently approved dose. In 2022, Biogen reported final data from Part A of the ongoing, three-part DEVOTE study. Results from Part A, an open-label safety evaluation period in children and teens with later-onset SMA, suggest that the higher dosing regimen of SPINRAZA leads to higher levels of the drug in the cerebrospinal fluid, or CSF, supporting further development of a higher dose of SPINRAZA. Additionally, the results indicated that SPINRAZA was generally well-tolerated.
- RESPOND: In the Phase 4 RESPOND study, Biogen is evaluating the benefit of SPINRAZA in infants and children with a suboptimal clinical response to the gene therapy, onasemnogene abeparvovec. In 2023, Biogen presented interim results from the RESPOND study that showed improved motor function in most participants treated with SPINRAZA following treatment with onasemnogene abeparvovec.
- ASCEND: In the Phase 3b ASCEND study, Biogen is evaluating the clinical outcomes and assessing the safety of a higher dose of SPINRAZA in children, teens and adults with later-onset SMA following treatment with risdiplam.

Additionally, Biogen continues to conduct the Phase 2 NURTURE study, an open-label study investigating the benefit of SPINRAZA when administered before symptom onset in patients genetically diagnosed with SMA, and likely to develop Type 1 or Type 2 SMA. NURTURE was the first study to investigate the potential to slow or stop SMA disease progression in presymptomatic SMA patients. In 2022, Biogen reported new NURTURE study data, showing that early and sustained treatment with SPINRAZA helped participants to maintain and/or make progressive gains in motor function. These data showed that after 11 months of additional follow-up since the 2020 interim analysis, all children who were able to walk alone maintained this ability and one child gained the ability to walk alone, increasing the total percentage of study participants able to walk from 92% to 96%. Further, most children achieved motor milestones within age-appropriate timelines and no major motor milestones were lost. The safety of SPINRAZA over this extended follow-up period was consistent with previously reported findings.

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

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

SOD1-ALS is a rare, fatal, neurodegenerative disorder caused by a mutation in the *SOD1* gene leading to a progressive loss of motor neurons. As a result, people with SOD1-ALS experience increasing muscle weakness, loss of movement, difficulty breathing and swallowing and eventually succumb to the disease. Current treatment options for people with SOD1-ALS are extremely limited. It is estimated that there are approximately 1,400 patients with SOD1-ALS in the G7 countries (comprised of Canada, France, Germany, Italy, Japan, the United Kingdom and the U.S.).

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

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

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

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

QALSODY had a favorable safety and tolerability profile.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

FCS is a rare, genetic disease estimated to affect one to two individuals per million and characterized by extremely elevated triglyceride levels, typically greater than 1,000 mg/dl. FCS can lead to many chronic health issues including severe, recurrent abdominal pain, fatigue, high risk of life-threatening pancreatitis and abnormal enlargement of the liver or spleen. In addition, people with FCS are often unable to work, adding to their disease burden. In severe cases, patients can have bleeding into the pancreas, serious tissue damage, infection, and cyst formation, as well as damage to other vital organs such as the heart, lungs, and kidneys.

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

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

Our Innovative Pipeline of Investigational Medicines

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

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

IONIS CLINICAL PIPELINE

MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
NEUROLOGICAL					
Zilganersen (GFAP)	Alexander disease	Ionis			
Ulefnersen	FUS-ALS	Ionis			
Tofersen	Presymptomatic SOD1-ALS	Biogen			
ION717 (PRNP)	Prion disease	Ionis			
IONIS-MAPT$_{Rx}$ (TAU)	Alzheimer's disease	Biogen			
ION859 (LRRK2)	Parkinson's disease	Biogen			
ION464 (SNCA)	MSA & Parkinson's disease	Biogen			
ION541 (ATXN2)	ALS	Biogen			
ION582 (UBE3A)	Angelman syndrome	Biogen			
Tominersen (HTT)	Huntington's Disease	Roche			
ION360 (SMN2)	Spinal Muscular Atrophy	Biogen			
CARDIOVASCULAR					
Eplontersen	ATTR-CM	Ionis/ AstraZeneca			
Olezarsen (APOC-III)	FCS	Ionis			
Olezarsen (APOC-III)	SHTG	Ionis			
Pelacarsen	Lp(a) CVD	Novartis			
Fesomersen (FXI)	Thrombotic disorders	Ionis			
ION904 (AGT)	Treatment-resistant hypertension	Ionis			
SPECIALTY RARE					
Donidalorsen (PKK)	HAE	Ionis[1]			
Sapablursen (TMPRSS6)	Polycythemia vera	Ionis			
OTHER MEDICINES FOR HIGH PATIENT NEED					
Bepirovirsen	HBV	GSK			
IONIS-FB-L$_{Rx}$	IgA Nephropathy	Roche			
IONIS-FB-L$_{Rx}$	Geographic Atrophy	Roche			
ION224 (DGAT2)	NASH	Ionis			
ION839 (PNPLA3)	NASH	AstraZeneca			

[1] Granted Otsuka exclusive rights to commercialize donidalorsen in Europe.

Our Phase 3 Pipeline

We currently have nine medicines in our Phase 3 pipeline:

[1] Granted Otsuka exclusive rights to commercialize donidalorsen in Europe.

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

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

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

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

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

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

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

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

We are also conducting ongoing Phase 3 studies for the expanded SHTG patient population. CORE and CORE2 are global, multi-center, randomized, double-blind, placebo-controlled studies enrolling approximately 540 and 390 patients, respectively, designed to assess the efficacy, safety and tolerability of olezarsen in patients with SHTG. The CORE and CORE2 studies compare olezarsen to placebo in patients with triglyceride levels equal to or greater than 500 mg/dL who are on currently available therapies for elevated triglycerides. The primary endpoint of the studies is the percent change in fasting triglycerides from baseline at month six. Additionally, in November 2022, we initiated ESSENCE, a global, multi-center, randomized, double-blind, placebo-controlled study enrolling approximately 1,300 patients to provide a robust safety database. The primary endpoint of the study is the percent change in fasting triglycerides from baseline at month six.

In January 2020, we reported positive results from a Phase 2 clinical study in patients with hypertriglyceridemia and at high risk of or with established CVD. Olezarsen achieved statistically significant, dose-dependent reductions in fasting triglycerides compared to placebo at all dose levels. Olezarsen also achieved statistical significance in numerous key secondary endpoints, including significant reductions in apoC-III. Olezarsen had a favorable safety and tolerability profile supportive of continued development.

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

Donidalorsen (PKK) – Donidalorsen (formerly IONIS-PKK-L_{Rx}) is an investigational LICA medicine we designed to inhibit the production of prekallikrein, or PKK. HAE is a rare genetic disease that is characterized by severe and potentially fatal swelling of the arms, legs, face and throat. PKK plays an important role in the activation of inflammatory mediators associated with acute attacks of HAE. By inhibiting the production of PKK, donidalorsen could be an effective prophylactic approach to preventing HAE attacks. It is estimated that there are more than 20,000 patients with HAE in the U.S. and Europe.

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

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

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

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

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

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

In December 2019, Novartis initiated the Phase 3 study of pelacarsen, Lp(a) HORIZON, in patients with elevated Lp(a) levels and a prior cardiovascular event. Lp(a) HORIZON is a global, multi-center, randomized, double-blind, placebo-controlled cardiovascular outcomes study in more than 8,000 patients designed to assess the efficacy, safety and tolerability of pelacarsen. Patients are treated with 80 mg of pelacarsen administered monthly by subcutaneous injection. The primary endpoint in Lp(a) HORIZON is the time to occurrence of first major adverse cardiovascular event, or MACE. In July 2022, we announced that the Lp(a) HORIZON study had completed enrollment.

In November 2018, at the American Heart Association, or AHA, annual meeting, we reported results of the Phase 2 study of pelacarsen in patients with hyperlipoproteinemia(a). In the Phase 2 study, we observed statistically significant and dose dependent reductions from baseline in Lp(a) levels. Approximately 98% of patients who received the highest dose in the study demonstrated a reduction in Lp(a) levels to below the recommended threshold for CVD events (<50 mg/dL). Pelacarsen had a favorable safety and tolerability profile supportive of continued development.

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

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

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

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

In April 2021, we initiated a pivotal study of zilganersen in patients with AxD and in September 2023, we advanced zilganersen into the Phase 3 portion of the pivotal study. The pivotal study of zilganersen is a multi-center, double-blind, placebo-controlled, multiple-ascending dose study in approximately 55 patients with AxD designed to assess the efficacy, safety and tolerability of zilganersen. Patients will receive zilganersen or placebo for a 60-week period, after which all patients in the study will receive zilganersen for a 60-week open-label treatment period. The primary endpoint is the change from baseline in the 10-Meter Walk Test, or 10MWT.

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

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

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

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

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

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

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

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

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

HBV infection is a serious health problem that can lead to significant and potentially fatal health conditions, including cirrhosis, liver failure and liver cancer. Chronic HBV infection is one of the most common persistent viral infections in the world, affecting nearly 300 million people and resulting in approximately 900,000 deaths annually. Currently available therapies, although effective in reducing circulating HBV in the blood, do not effectively inhibit HBV antigen production and secretion, which are associated with poor prognosis and increased risk of liver cancer.

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

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

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

In August 2019, GSK exercised its option to license our HBV program following the positive results of the Phase 2a study of bepirovirsen in patients with chronic HBV infection. As a result, GSK is responsible for global development, regulatory and commercialization activities, and costs for the HBV program.

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

IONIS-FB-L$_{Rx}$ (IgAN) (RG6299) – IONIS-FB-L$_{Rx}$ is an investigational LICA medicine we designed to inhibit the production of complement factor B, or FB, and the alternative complement pathway. Genetic association studies have shown that overaction of the alternative complement pathway has been associated with the development of several complement-mediated diseases, including IgAN. As discussed below under the "IONIS-FB-L$_{Rx}$" section in our "Other Medicines in Development" section, we are also developing IONIS-FB-L$_{Rx}$ for GA, secondary to age-related macular degeneration, or AMD.

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

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

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

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

Our Neurological Medicines in Development

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

MEDICINES	INDICATION	PARTNER	PHASE 1	PHASE 2	PHASE 3
NEUROLOGICAL PIPELINE					
Zilganersen (GFAP)	Alexander disease	Ionis			
Ulefnersen	FUS-ALS	Ionis			
Tofersen	SOD1-ALS	Biogen			
ION717 (PRNP)	Prion disease	Ionis			
IONIS-MAPT$_{Rx}$ (TAU)	Alzheimer's disease	Biogen			
ION859 (LRRK2)	Parkinson's disease	Biogen			
ION464 (SNCA)	MSA & Parkinson's disease	Biogen			
ION541 (ATXN2)	ALS	Biogen			
ION582 (UBE3A)	Angelman syndrome	Biogen			
Tominersen (HTT)	Huntington's Disease	Roche			

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

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

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

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

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

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

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

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

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

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

In December 2019, Biogen exercised its option to license IONIS-MAPT$_{Rx}$. Biogen has responsibility for global development, regulatory and commercialization activities, and costs for IONIS-MAPT$_{Rx}$.

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

In August 2019, Biogen initiated a Phase 1/2 study evaluating ION859 in patients with PD. The Phase 1/2 study is a global, multi-center, randomized, double-blinded, placebo-controlled study in approximately 80 patients designed to assess the safety, tolerability and activity of multiple ascending doses of ION859 administered intrathecally.

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

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

In July 2020, we initiated a Phase 1/2 study evaluating ION464 in patients with MSA. The current study is a multi-center, randomized, double-blinded, placebo-controlled study in approximately 40 patients designed to assess the safety and tolerability of multiple ascending doses of ION464 administered intrathecally.

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

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

In October 2020, Biogen initiated a Phase 1/2 clinical study evaluating ION541 in patients with ALS. The current study is a randomized, blinded, placebo-controlled study in approximately 110 patients designed to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of ION541 administered intrathecally.

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

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

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

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

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

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

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

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

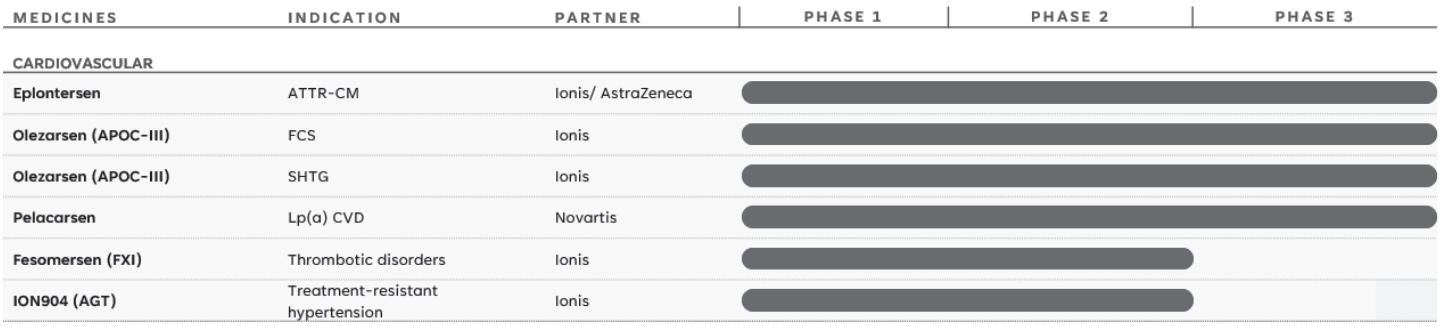
Roche conducted the Phase 3 study, GENERATION HD1, of tominersen in patients with HD. The Phase 3 study was a randomized, multicenter, double-blind, placebo-controlled study that recruited 791 participants. In March 2021, Roche announced that dosing would be stopped in the study following a recommendation from the independent data monitoring committee, or iDMC, based on an overall benefit/risk assessment. In January 2022, Roche announced findings from a post-hoc analysis of the GENERATION HD1 study that suggested tominersen may benefit younger adult patients with lower disease burden.

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

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

Our Cardiovascular Medicines in Development

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



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

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

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

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

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

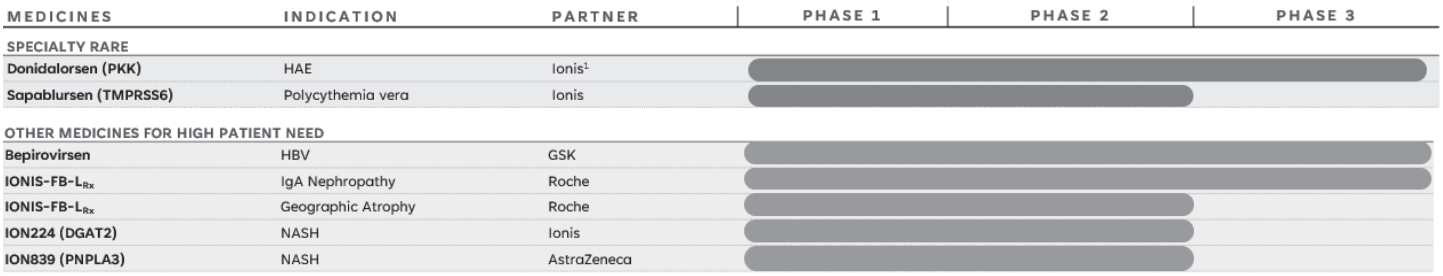
In November 2022, we regained all rights to fesomersen, which we had previously licensed to Bayer in February 2017.

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

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

Other Medicines for High Patient Need in Development

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



1. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe.

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

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

PV is a rare disease driven by a mutation in the *JAK2* gene that is potentially fatal and characterized by overproduction of red blood cells. This overproduction leads to a thickening of the blood, which increases patients' risk of life-threatening blood clots, including in the lungs, heart and brain. Patients with PV also experience severe iron deficiency and symptoms such as fatigue and impaired cognitive function. There are no approved disease-modifying treatments for PV.

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

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

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

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

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

ION224 (DGAT2) – ION224 is an investigational LICA medicine we designed to reduce the production of diacylglycerol acyltransferase 2, or DGAT2, to treat patients with nonalcoholic steatohepatitis, or NASH. NASH is a common liver disease characterized by liver steatosis, inflammation and scarring and can lead to increased risk of CVD, liver cancer, need for liver transplantation and early death. DGAT2 is an enzyme that catalyzes the final step in triglyceride synthesis in the liver. Reducing the production of DGAT2 should therefore decrease triglyceride synthesis in the liver. In animal studies, antisense inhibition of DGAT2 significantly improved liver steatosis, lowered blood lipid levels and reversed diet-induced insulin resistance.

Nonalcoholic fatty liver disease, or NAFLD, describes the full spectrum of liver disease progression from fatty liver to NASH to cirrhosis to hepatocellular carcinoma. NASH epidemiology studies have estimated 13% to 32% of the global population has NAFLD, 1.5% to 6.5% have NASH, and up to 10% of NASH patients progress to advanced liver disease. There are currently no commercially available medications to treat NASH.

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

In June 2021, we initiated a Phase 2 study of ION224 in patients with confirmed non-alcoholic steatohepatitis. The Phase 2 study is a multi-center, randomized, double-blind, placebo-controlled clinical study in approximately 160 patients designed to assess the efficacy, safety and tolerability of multiple subcutaneous doses of ION224 on NASH histologic improvement.

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

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

In June 2019, we initiated a Phase 2 GOLDEN study evaluating IONIS-FB-L$_{Rx}$ in patients with GA secondary to AMD. The study is a randomized, masked, placebo-controlled study in approximately 330 patients designed to assess the efficacy, safety and tolerability of multiple ascending doses of IONIS-FB-L$_{Rx}$ administered subcutaneously in adults with GA. The primary endpoint is the absolute change from baseline in GA area at week 49. In August 2023, we announced that the GOLDEN study had completed enrollment.

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

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

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

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

Our Technology

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

Overview of Ionis' Technology

All of the medicines currently in our clinical pipeline use our antisense technology — an innovative platform for discovering first-in-class and/or best-in-class medicines. Antisense medicines target RNA, the intermediary that conveys genetic information from a gene to the protein synthesis machinery in the cell. By targeting RNA instead of proteins, we can use antisense technology to increase, decrease or alter the production of specific proteins. Most of our antisense medicines are designed to bind to mRNAs and inhibit the production of disease-causing proteins. Examples of these include WAINUA, olezarsen and donidalorsen. SPINRAZA is an example of an antisense medicine that modulates RNA splicing to increase protein production of the SMN protein, which is critical to the health and survival of nerve cells in the spinal cord that are responsible for neuro-muscular function. The SMN protein is deficient in people with SMA. Our antisense technology is also broadly applicable to many additional antisense mechanisms including decreasing toxic RNAs.

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

Our advanced LICA technology is a chemical technology we developed that involves attaching a molecule called a ligand that binds with receptors on the surface of cells in a highly specific manner. Because these receptors are often found only on certain cell types, LICA allows us to increase effective delivery of our antisense medicines with higher specificity to certain cell types that express these receptors relative to non-conjugated antisense medicines. We currently have an integrated assessment of data from multiple LICA medicines and clinical programs which demonstrates that our LICA technology for liver targets can increase potency by 20-30-fold over our non-LICA antisense medicines. Our LICA medicines have also demonstrated consistently favorable safety and tolerability in clinical trials, including in our Phase 3 studies of WAINUA (for ATTRv-PN), olezarsen (for FCS patients) and donidalorsen (for HAE).

Emerging Technology Advancements

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

Mesyl phosphoramidate Backbone Chemistry

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

Bicycle Collaboration

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

Gene Editing and Metagenomi Collaboration

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

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

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

Collaborative Arrangements

We have established alliances with a cadre of leading global pharmaceutical companies. Our partners include the following companies, among others: AstraZeneca, Biogen, GSK, Novartis, Otsuka and Roche. Through our partnerships, we have earned both commercial revenue and a broad and sustaining base of R&D revenue in the form of license fees, upfront payments and milestone payments. In addition, we are eligible to receive royalties under our partnerships. Below, we include the significant terms of our collaboration agreements. For additional details, including other financial information, refer to Part IV, Item 15, Note 4, *Collaborative Arrangements and Licensing Agreements,* in the Notes to the Consolidated Financial Statements.

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. These collaborations combine our expertise in creating antisense medicines with Biogen's expertise in developing therapies for neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with SMA. In April 2023, the FDA granted accelerated approval for QALSODY (tofersen) in the U.S. to treat patients with SOD1-ALS. Biogen developed QALSODY under our 2013 strategic neurology collaboration. In addition, we and Biogen are currently developing numerous other investigational medicines to treat neurodegenerative diseases, including medicines in development to treat people with ALS, SMA, AS, AD, and PD. From inception through December 31, 2023, we have generated more than $3.8 billion in payments from our Biogen collaborations.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA, an RNA-targeted therapy for the treatment of SMA. We are receiving tiered royalties ranging from 11 percent to 15 percent on sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Under our agreement, Biogen is responsible for global development, regulatory and commercialization activities and costs for SPINRAZA. From inception through December 31, 2023, we recognized more than $2.0 billion in total revenue under our SPINRAZA collaboration, including more than $1.6 billion in revenue from SPINRAZA royalties and more than $425 million in R&D revenue.

New antisense medicines for the treatment of SMA

In 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies.

In 2021, Biogen exercised its option to license ION306. Biogen is solely responsible for the costs and expenses related to the development, manufacturing and potential future commercialization of ION306 following the option exercise. We will receive development and regulatory milestone payments from Biogen if new medicines, including ION306, advance towards marketing approval.

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

Neurology Collaborations

2018 Strategic Neurology

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

For each medicine under this collaboration, we are eligible to receive a license fee, development milestone payments and regulatory milestone payments. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration. We are currently advancing multiple programs under this collaboration. From inception through December 31, 2023, we have generated nearly $1.1 billion in payments under this collaboration.

2013 Strategic Neurology

In 2013, we and Biogen entered into a strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. In most cases, we are responsible for drug discovery and early development of antisense medicines and Biogen has the option to license antisense medicines after Phase 2 proof-of-concept. In 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine.

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

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

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

For each of the other antisense molecules that are chosen for drug discovery and development under this collaboration, we are eligible to receive a license fee, development milestone payments and regulatory milestone payments. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that Biogen successfully commercializes under this collaboration. From inception through December 31, 2023, we have generated more than $325 million in payments under our 2013 strategic neurology collaboration.

2012 Neurology

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

For each program under this collaboration, we are eligible to receive a license fee, development milestone payments and regulatory milestone payments, plus a mark-up on the costs of the Phase 1 and 2 studies. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that Biogen successfully commercializes under this collaboration. From inception through December 31, 2023, we have generated more than $230 million in payments under this collaboration.

Joint Development and Commercialization Arrangement

AstraZeneca

WAINUA (Eplontersen) Collaboration

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

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

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

Research and Development Partners

AstraZeneca

In addition to our collaboration for WAINUA, we have a collaboration with AstraZeneca focused on discovering and developing treatments for cardiovascular, renal and metabolic diseases, which we formed in 2015. Under our collaboration, AstraZeneca has licensed multiple medicines from us. AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for each of the medicines it has licensed from us.

Over the term of the collaboration, we are eligible to receive an upfront payment, license fees, development milestone payments and regulatory milestone payments. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through December 31, 2023, we have generated more than $340 million in payments under this collaboration.

GSK

In 2010, we entered into a collaboration with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for serious and rare diseases, including infectious diseases. Under our collaboration, GSK is developing bepirovirsen for the treatment of chronic HBV infection. In 2019, following positive Phase 2 results, GSK licensed our HBV program. GSK is responsible for all global development, regulatory and commercialization activities and costs for the HBV program.

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

Novartis

Pelacarsen Collaboration

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

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

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

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

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

Roche

Huntington's Disease

In 2013, we entered into an agreement with Hoffmann-La Roche Inc and F. Hoffmann-La Roche Ltd, collectively Roche, to develop treatments for HD based on our antisense technology. Under the agreement, we discovered and developed tominersen, an investigational medicine targeting HTT protein. We developed tominersen through completion of our Phase 1/2 clinical study in people with early-stage HD. In 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen. As a result, Roche is responsible for all global development, regulatory and commercialization activities and costs for tominersen.

Over the term of the collaboration, we are eligible to receive a license fee, development milestone payments, regulatory milestone payments and sales milestone payments as tominersen advances. In addition, we are eligible to receive milestone payments for each additional medicine successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on net sales of any product resulting from this collaboration. From inception through December 31, 2023, we have generated more than $150 million in payments under this collaboration.

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

In 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. We are currently conducting Phase 2 studies in two disease indications for IONIS-FB-L_{Rx}, one for the treatment of patients with IgAN and one for the treatment of patients with GA, the advanced stage of dry AMD. In April 2023, Roche initiated a Phase 3 study of IONIS-FB-L_{Rx} in patients with IgAN.

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

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

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

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

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

Commercialization Partnerships

Otsuka

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

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

PTC Therapeutics

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

Swedish Orphan Biovitrum AB (Sobi)

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

Technology Enhancement Collaborations

Bicycle Therapeutics

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

Metagenomi

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

Vect-Horus

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

Other Agreements

Alnylam Pharmaceuticals, Inc.

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

Manufacturing

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

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

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

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

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

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

SPINRAZA

Biogen is responsible for SPINRAZA drug supply.

QALSODY

Biogen is responsible for QALSODY drug supply.

WAINUA

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

TEGSEDI and WAYLIVRA

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

Olezarsen, Donidalorsen, Zilganersen, Ulefnersen

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

Pelacarsen

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

Bepirovirsen

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

IONIS-FB-L_{Rx}

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

Commercial Operations

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

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

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

Medical Affairs

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

Intellectual Proprietary Rights

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

Product-Specific IP

Each of our medicines is protected worldwide by product-specific patents claiming oligonucleotides having the nucleobase sequences and chemical modifications of our medicines; and methods of achieving cellular or clinical endpoints using such oligonucleotides. We pursue such patents in significant markets and/or countries for each medicine in development. We also seek to maximize patent term. In some cases, the patent term can be extended to recapture a portion of the term lost during regulatory review. Expiration dates listed below do not reflect any such extensions.

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

Marketed Products

SPINRAZA and Survival Motor Neuron 2

Patents

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

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

Trademarks

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

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

QALSODY and SOD-1

Patents

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

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

Trademarks

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

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

WAINUA and Transthyretin

Patents

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

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

Trademarks

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

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

TEGSEDI and Transthyretin

Patents

We believe TEGSEDI (inotersen) is protected from generic competition in the U.S. and Europe until at least 2031. The table below lists some key issued patents protecting TEGSEDI in the U.S. and Europe:

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

Trademarks

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

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

WAYLIVRA and Apolipoprotein C-III

Patents

We believe WAYLIVRA (volanesorsen) is protected from generic competition in Europe until at least 2034. We have obtained patent claims in the U.S. and Europe drawn to the use of antisense compounds complementary to a broad active region of human apoC-III, including the site targeted by WAYLIVRA. We have also obtained issued patents claiming the specific sequence and chemical composition of WAYLIVRA in the U.S. and Europe. The table below lists some key issued patents protecting WAYLIVRA in the U.S. and Europe:

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

Trademark

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

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

Phase 3 Programs

Olezarsen and ApoC-III

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

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

Donidalorsen and PKK

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

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

Zilganersen and GFAP

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

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

Ulefnersen and FUS

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

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

Pelacarsen and Apo(a)

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

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

Bepirovirsen and Hepatitis B Virus

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

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

IONIS-FB-L_{Rx} and Factor B

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

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

Platform IP

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

Chemically Modified Nucleosides and Oligonucleotides

The most broadly applicable of our patents are those that claim modified nucleosides and oligonucleotides comprising the modified nucleosides that we incorporate into our medicines to increase their therapeutic efficacy. The following are some of our patents in this category in the U.S. and Europe:

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	7,399,845	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
United States	7,741,457	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
United States	8,022,193	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Oligonucleotides containing cEt nucleoside analogs
Europe	1984381	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	cEt nucleosides and oligonucleotides containing these nucleoside analogs
Europe	2314594	6-MODIFIED BICYCLIC NUCLEIC ACID ANALOGS	2027	Oligonucleotides containing cEt nucleoside analogs and methods of use
United States	7,569,686	COMPOUNDS AND METHODS FOR SYNTHESIS OF BICYCLIC NUCLEIC ACID ANALOGS	2027	Methods of synthesizing cEt nucleosides
Europe	2092065	ANTISENSE COMPOUNDS	2027	Gapmer oligonucleotides having 2’-modifed and LNA nucleosides
Europe	2410053	ANTISENSE COMPOUNDS	2027	Gapmer oligonucleotides having wings comprised of 2’-MOE and bicyclic nucleosides
Europe	2410054	ANTISENSE COMPOUNDS	2027	Gapmer oligonucleotides having a 2’-modifed nucleoside in the 5’-wing and a bicyclic nucleoside in the 3’-wing
United States	9,550,988	ANTISENSE COMPOUNDS	2028	Gapmer oligonucleotides having BNA nucleosides and 2’-MOE nucleosides
United States	10,493,092	ANTISENSE COMPOUNDS	2028	Gapmer oligonucleotides having BNA nucleosides and 2’-MOE nucleosides and/or 2’-OMe nucleosides
Europe	3067421	OLIGOMERIC COMPOUNDS COMPRISING BICYCLIC NUCLEOTIDES AND USES THEREOF	2032	Gapmer oligonucleotides having at least one bicyclic, one 2’-modified nucleoside and one 2’-deoxynucleoside
United States	11,629,348	LINKAGE MODIFIED OLIGONUCLEOTIDES AND USES THEREOF	2040	Gapmer oligonucleotides having 2-4 mesyl phosphoramidate internucleoside linkages at specified positions in the gap

LIgand-Conjugated Antisense (LICA) Technology

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

Jurisdiction	Patent No.	Title	Expiration	Description of Claims
United States	9,127,276	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Preferred THA LICA conjugated to any group of nucleosides, including gapmers, double-stranded siRNA compounds, and fully modified oligonucleotides
United States	9,181,549	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Preferred THA conjugate having our preferred linker and cleavable moiety conjugated to any oligomeric compound or any nucleoside having a 2'-MOE modification or a cEt modification
Europe	2991661	CONJUGATED ANTISENSE COMPOUNDS AND THEIR USE	2034	Preferred THA LICA conjugated to any group of nucleosides, including gapmers, double-stranded siRNA compounds, and fully modified oligonucleotides

Manufacturing

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

Government Regulation

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

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

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

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

Pricing and Reimbursement

For any approved medicine, domestic and foreign sales of the medicine depend, in part, on the availability and amount of coverage and adequate reimbursement by third-party payers, including governments and private health plans. The process for determining whether a payer will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payer will pay for the product, or procedures that utilize such product. Private health plans may seek to manage cost and use of our medicines by implementing coverage and reimbursement limitations. For example, third-party payers may limit coverage to specific products on an approved list, or formulary, which might not include all U.S. FDA-approved products for a particular indication. Moreover, a payer's decision to provide coverage for a medicine does not imply that an adequate reimbursement rate will be approved. Additionally, coverage and reimbursement for drugs can differ significantly from payer to payer. One third-party payer's decision to cover a particular medicine does not ensure that other payers will also provide coverage for the medicine or will provide coverage at an adequate reimbursement rate.

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

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

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

Healthcare Reform

Both the federal and state governments in the U.S. and foreign governments continue to propose and pass new legislation and regulations designed to contain or reduce the cost of healthcare. For example, in July 2021, the Biden administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In response to Biden’s executive order, on September 9, 2021, the U.S. Department of Health and Human Services, or HHS, released a report that outlined principles for drug pricing reform and set out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS could take to advance these principles. Congress is also considering additional health reform measures that may result in decreased reimbursement, which may further exacerbate industry-wide pressure to reduce the prices charged for medical products.

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

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

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

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

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

Sales and Marketing

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

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

Given the significant penalties and fines that can be imposed on companies and individuals if convicted, allegations of such violations often result in settlements even if the company or individual being investigated admits no wrongdoing. Settlements often include significant civil sanctions, including fines and civil monetary penalties, corporate integrity agreements, and could include criminal penalties. If the government were to allege or convict us or our executive officers of violating these laws, our business could be harmed. In addition, private individuals can bring similar actions. Our activities could be subject to challenge for the reasons discussed above and due to the broad scope of these laws and the increasing attention being given to them by law enforcement authorities. As described above, other healthcare laws that may affect our ability to operate include HIPAA, analogous state laws governing the privacy and security of health information, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, and the Physician Payments Sunshine Act. Further, there are an increasing number of state laws that require manufacturers to make reports to states on pricing and marketing information. Many of these laws contain ambiguities as to what is required to comply with the laws. Given the lack of clarity in laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent state authorities.

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

As discussed above, both the federal and state governments in the U.S. and foreign governments continue to propose and pass new legislation and regulations designed to contain or reduce the cost of healthcare, including new models aimed to lower of cost of drugs, promote accessibility, and improve quality of care and initiatives to control the price of prescription drugs using march-in rights under the Bayh-Dole Act.

The Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits certain individuals and entities, including us, from promising, paying, offering to pay, or authorizing the payment of anything of value to any foreign government official, directly or indirectly, to obtain or retain business or an improper advantage. If we violate the FCPA, it could result in large civil and criminal penalties as well as an adverse effect on our reputation, operations, and financial condition. We could also face collateral consequences such as debarment and the loss of export privileges. In addition, in many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, any dealings with these prescribers and purchasers may be subject to regulation under the FCPA. There is no certainty that all employees and third-party business partners (including our contract research organizations, contract manufacturing organizations, distributors, wholesalers, agents, contractors and other partners) will comply with anti-bribery laws. Importantly, we do not control the actions of manufacturers and other third-party agents, although we may be liable for their actions.

Competition

Our Business in General

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

Our commercial medicines and our medicines in development address numerous markets. The diseases our medicines target for which we have or may receive marketing authorization will determine our competition. For some of our medicines, an important factor may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop medicines, complete the clinical trials and marketing authorization processes and supply commercial quantities of the medicines to the market are important competitive factors. We expect to compete with products approved for sale based on a variety of factors, including, among other things, product efficacy, safety, mechanism of action, dosing administration, marketing and sales strategy and tactics, availability, price, and reimbursement.

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

SPINRAZA

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

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
Zolgensma (Onasemnogene abeparvovec)	Novartis	Gene therapy targeting the genetic root cause of SMA by replacing the missing or nonworking SMN1 gene	Approved for pediatric SMA patients less than 2 years of age	Intravenous infusion
Evrysdi (Risdiplam)	Roche	A small molecule medicine that modulates splicing of the SMN2 gene	Approved for SMA in pediatric and adult patients	Oral
OAV101 (Onasemnogene abeparvovec)	Novartis	Gene therapy targeting the genetic root cause of SMA by replacing the missing or nonworking SMN1 gene	Phase 3	Intrathecal injection

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

QALSODY

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

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

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

WAINUA and TEGSEDI

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

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
Onpattro (Patisiran)	Alnylam	An RNAi medicine formulated with lipid nanoparticles to inhibit TTR mRNA	Received CRL in the U.S. for ATTR-CM Approved in US, EU, Japan and select other markets for ATTRv-PN	Intravenous infusion
Vyndaqel/Vyndamax (Tafamidis and tafamidis meglumine)	Pfizer	A small molecule medicine to stabilize TTR protein	Approved in EU, Japan and select other markets for ATTRv-PN, ATTR-CM; indications vary by region	Oral
Amvuttra (Vutrisiran)	Alnylam	An RNAi medicine conjugated with GalNAc to inhibit TTR mRNA	Approved for ATTRv-PN in the U.S., EU and Japan, Phase 3 for ATTR-CM	Subcutaneous Injection
Acoramidis	BridgeBio	Small molecule that binds and stabilizes TTR in the blood	Submitted in U.S., EU and Japan	Oral
NTLA-2001	Intellia/ Regeneron	CRISPR therapeutic candidate designed to reduce circulating TTR protein levels	Phase 3 ATTR-CM	Intravenous Infusion
ALXN2220	AstraZeneca	A monoclonal IgG1 which acts by targeting and depleting TTR protein	Phase 3 ATTR-CM	Intravenous Infusion
NNC6019-0001	Novo Nordisk	A monoclonal antibody to deplete amyloid via antibody-mediated phagocytosis	Phase 2 ATTR-CM	Intravenous Infusion

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

WAYLIVRA and Olezarsen

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

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
ARO-APOC3 (Plozasiran)	Arrowhead	Targets APOCIII by utilizing Targeted RNAi Molecule Platform	Phase 3 FCS, Phase 2 SHTG	Subcutaneous Injection
Pegozafermin	89bio	FGF21 analog	Phase 3 SHTG	Subcutaneous Injection

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

Donidalorsen

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

Medicine	Company	Medicine Description [1]	Phase [1]	Route of Administration [1]
Takhzyro (lanadelumab-flyo)	Takeda	A monoclonal antibody that inhibits plasma kallikrein activity	Approved for HAE patients two years and older	Subcutaneous Injection
Cinryze (C1 esterase inhibitor)	Takeda	A human plasma protein that mediates inflammation and coagulation	Approved for HAE patients six years and older	Intravenous Infusion
Orladeyo (berotralstat)	BioCryst	Oral plasma kallikrein inhibitor	Approved for HAE patients 12 years and older	Oral
Haegarda (C1 esterase inhibitor)	CSL Behring	C1 esterase inhibitor	Approved for HAE patients 6 years and older	Subcutaneous Injection
Garadacimab	CSL Behring	An anti-factor XIIa monoclonal antibody	Under regulatory review in the U.S. and EU	Subcutaneous Injection
Deucrictibant	Pharvaris	An oral B2-receptor antagonist	Phase 2	Oral
STAR-0215	Astria	A monoclonal antibody inhibitor of plasma kallikrein	Phase 2	Subcutaneous Injection
NTLA-2002	Intellia	CRISPR therapeutic candidate designed to inactivate the kallikrein B1 gene	Phase 1/2	Intravenous Infusion

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

Zilganersen

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

Ulefnersen

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

Pelacarsen

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

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

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

Bepirovirsen

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

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

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

IONIS-FB-L_{Rx}

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

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

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

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

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

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

Corporate Responsibility and Environmental, Social and Governance Initiatives

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

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

Ionis Corporate Responsibility Strategic Pillars

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

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

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

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

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

Employees and Human Capital

As of February 15, 2024, we employed 927 people, the vast majority of whom reside in the U.S. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Our average employee turnover rate in 2023 was 7 percent, while the turnover for life sciences and medical device companies over this period was 23 percent according to a survey published by Radford – an Aon Hewitt Company. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is as critical to our future success as it has been to the success we have enjoyed to date.

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

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

Benefits

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

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

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

Pay Equity

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

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

Diversity, Equity and Inclusion

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

Training and Development

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

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

Information about our Executive Officers

The following sets forth certain information regarding our executive officers as of February 15, 2024:

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

BRETT P. MONIA, Ph.D.

Chief Executive Officer

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

JOSEPH T. BAROLDI, M.A., M.B.A., M.S.

Executive Vice President, Chief Business Officer

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

BRIAN BIRCHLER

Executive Vice President, Corporate and Development Operations

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

C. FRANK BENNETT, Ph.D.

Executive Vice President, Chief Scientific Officer

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

ONAIZA CADORET-MANIER

Executive Vice President, Chief Global Product Strategy and Operations Officer

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

RICHARD S. GEARY, Ph.D.

Executive Vice President, Chief Development Officer

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

ELIZABETH L. HOUGEN

Executive Vice President, Finance and Chief Financial Officer

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

PATRICK R. O'NEIL, Esq.

Chief Legal Officer, General Counsel and Corporate Secretary

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

EUGENE SCHNEIDER, M.D.

Executive Vice President, Chief Clinical Development and Operations Officer

Dr. Schneider has served as Ionis' Executive Vice President and Chief Clinical Development and Operations Officer since September 2023. From January 2021 to September 2023, Dr. Schneider served as our Executive Vice President and Chief Clinical Development Officer. From August 2018 to December 2020, Dr. Schneider served as our Senior Vice President, Head of Clinical Development. From April 2015 to July 2018, Dr. Schneider was our Vice President, Clinical Development, Severe and Rare Diseases. Dr. Schneider joined Ionis in December 2013 as Executive Director, Clinical Development. Dr. Schneider has two decades of experience in clinical development primarily in the rare diseases space. Prior to joining Ionis, Dr. Schneider was senior medical director at both Synageva BioPharma and Biovail Technologies Ltd.

ERIC E. SWAYZE, Ph.D.

Executive Vice President, Research

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

Item 1A. RISK FACTORS

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

Risks Related to the Commercialization of our Medicines

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

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

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

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

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

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

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

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

For example, TEGSEDI requires periodic blood and urine monitoring and is available in the U.S. only through a risk evaluation and mitigation strategy, or REMS program. In addition, the product label for TEGSEDI in the U.S. has a boxed warning for thrombocytopenia and glomerulonephritis. Our main external competitors in the U.S. market for TEGSEDI are patisiran and vutrisiran, both marketed by Alnylam Pharmaceuticals, Inc. Neither patisiran nor vutrisiran has a boxed warning nor does either require use of a REMS program. Additionally, the product label for WAYLIVRA in the European Union, or EU, requires regular blood monitoring. In each case, these label requirements have negatively affected our ability to attract and retain patients for these medicines.

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

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

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

Further, we believe that future coverage, reimbursement and pricing will likely be subject to increased restrictions both in the U.S. and in international markets. In the U.S., recent health reform measures have resulted in reductions in Medicare and other healthcare funding, and there have been several recent U.S. Congressional inquiries, legislation and executive orders designed to, among other things, reduce drug prices, increase competition (including by enhancing support for generic and biosimilar drugs), lower out-of-pocket drug costs for patients, curtail spread pricing practices by pharmacy benefit managers, and foster scientific innovation to promote better health care and improved health. In addition, the Inflation Reduction Act of 2022, or the IRA, includes key actions aimed at reducing the costs of prescription drugs and allows HHS to negotiate the price of certain single-source drugs covered under Medicare and establish a price cap on such drugs. Specifically, in an effort to curb Medicare patients' out-of-pocket costs for prescription drugs, the Part D redesign legislation under the IRA requires, among other things, (1) a cap on out-of-pocket drug spending under Part D, (2) drug manufacturers to pay a rebate to the federal government if prices for drugs covered under Part D and Part B increase faster than the rate of inflation, and (3) drug manufacturers to contribute to the catastrophic coverage phase for Part D drugs as discounts through a manufacturer discount program. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions take effect progressively starting in fiscal year 2023. On August 29, 2023, HHS announced the list of the first ten drugs that will be subject to price negotiations, although the Medicare drug price negotiation program is currently subject to legal challenges. In response to the Biden administration's October 2022 executive order, on February 14, 2023, HHS released a report outlining three new models for testing by the CMS Innovation Center which will be evaluated on their ability to lower the cost of drugs, promote accessibility, and improve quality of care. It is unclear whether the models will be utilized in any health reform measures in the future. Further, on December 7, 2023, the Biden administration announced an initiative to control the price of prescription drugs using march-in rights under the Bayh-Dole Act. On December 8, 2023, the National Institute of Standards and Technology published for comment a Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights which for the first time includes the price of a product as one factor an agency can use when deciding to exercise march-in rights. While march-in rights have not previously been exercised, it is uncertain if that will continue under the new framework. It is unclear whether or how these selected models or similar policy initiatives will impact prescription drug pricing in the future.

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

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. For example, on January 5, 2024, the FDA approved Florida's Section 804 Importation Program, or SIP, proposal to import certain drugs from Canada for specific state healthcare programs. It is unclear how this program will be implemented, including which drugs will be chosen, and whether it will be subject to legal challenges in the United States or Canada. Other states have also submitted SIP proposals that are pending review by the FDA. Any such approved importation plans, when implemented, may result in lower drug prices for products covered by those programs. Third-party coverage and reimbursement for medicines may not be available or adequate in either the U.S. or international markets, which would negatively affect the potential commercial success of our products, our revenue and our profits.

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

Our competitors engage in drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. In addition, other companies are engaged in developing RNA-targeted technology. Our competitors may succeed in developing medicines that are:

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

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

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

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

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

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

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

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

Our medicines could be subject to regulatory limitations following approval.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

If we are not successful in expanding our manufacturing capabilities or cannot manufacture our medicines or contract with a third party to manufacture our medicines at costs that allow us to charge competitive prices to buyers, we cannot market our products profitably.

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

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

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

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

Risks Related to the Development and Regulatory Approval of our Medicines

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

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

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

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

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

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

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

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

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

Successful results in preclinical or initial human clinical studies, including the Phase 2 results for some of our medicines in development, may not predict the results of subsequent clinical studies. If any of our medicines in Phase 3 clinical studies do not show sufficient efficacy in patients with the targeted indication, or if such studies are discontinued for any other reason, it could negatively impact our development and commercialization goals for these medicines and our stock price could decline.

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

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

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

Further, the FDA or other regulatory authorities could request, among other things, additional information or commitments before we can start or continue a clinical study, protocol amendments, increased safety monitoring, additional product labeling information, and post-approval commitments. This happened in connection with the conditional marketing approval for WAYLIVRA in the EU, as the EC is requiring us to conduct a post-authorization safety study to evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients taking WAYLIVRA. In addition, under accelerated approval the FDA is requiring completion of the ongoing Phase 3 trial for QALSODY to confirm the clinical benefit of QALSODY.

Moreover, our commercial medicines are chemically similar to each other. As a result, a safety observation we encounter with one of our medicines could have, or be perceived by a regulatory authority to have, an impact on a different medicine we are developing. This could cause the FDA or other regulators to ask questions or take actions that could harm or delay our ability to develop and commercialize our medicines or increase our costs. Any failure or delay in our clinical studies could reduce the commercial potential or viability of our medicines.

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

We depend on independent clinical investigators, contract research organizations and other third-party service providers to conduct our clinical studies for our medicines and expect to continue to do so in the future. For example, we use clinical research organizations, such as Icon Clinical Research Limited, Medpace, Inc., Parexel International Corporation, Syneos Health, Inc. and Thermo Fisher Scientific Inc. for the clinical studies for our medicines, including WAINUA for the treatment of ATTR-CM, donidalorsen, olezarsen, ulefnersen and zilganersen. We rely heavily on these parties for successful execution of our clinical studies, but do not control many aspects of their activities. For example, the investigators are not our employees, but we are responsible for ensuring that such investigators conduct each of our clinical studies in accordance with the general investigational plan and approved protocols for the study. Third parties may not complete activities on schedule or may not conduct our clinical studies in accordance with regulatory requirements or our stated protocols. For example, some of our key vendors have in the past experienced labor shortages, which impacted their ability to perform services for us for certain of our clinical trials. Subsequent failures of these third parties to carry out their obligations, or a termination of our relationship with such third parties, could delay or prevent the development, marketing authorization and commercialization of our medicines.

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

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

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

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

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

If any of these pharmaceutical companies stops developing and funding these medicines, our business could suffer and we may not have, or be willing to dedicate, the resources available to develop these medicines on our own. Our collaborators can terminate their relationships with us under certain circumstances, many of which are outside of our control. For example, in 2022, Pfizer and Bayer decided to discontinue the clinical development programs for vupanorsen and fesomersen, respectively.

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

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

- conduct clinical studies;
- seek and obtain marketing authorizations; and
- manufacture and commercialize our medicines.

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

For example, a collaborator such as AstraZeneca, Biogen, GSK, Novartis, Otsuka or Roche, could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the medicine that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our medicines than it does to its own medicines.

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our medicines, including QALSODY, SPINRAZA, WAINUA, bepirovirsen, donidalorsen, IONIS-FB-L_{Rx} and pelacarsen.

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

In the U.S., under the Orphan Drug Act, the FDA may designate a medicine as an orphan drug if it is intended to treat a rare disease or condition affecting fewer than 200,000 individuals in the U.S. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process, but it can provide financial incentives, such as tax advantages and user-fee waivers, as well as longer regulatory exclusivity periods. The FDA has granted orphan drug designation to olezarsen for the treatment of patients with FCS, to ulefnersen for the treatment of patients with FUS-ALS, and to ION582 for the treatment of patients with Angelman syndrome. The FDA and EMA have granted orphan drug designation to WAINUA for the treatment of patients with ATTR, to donidalorsen for the treatment of patients with HAE, to TEGSEDI for the treatment of patients with ATTRv-PN, to WAYLIVRA for the treatment of patients with FCS, to tominersen for the treatment of patients with HD, and to ION356 for the treatment of patients with Pelizaeus-Merzbacher disease. In addition, the EMA has granted orphan drug designation to WAYLIVRA for the treatment of patients with FPL. Even if approval is obtained on a medicine that has been designated as an orphan drug, we may lose orphan drug exclusivity if the FDA or EMA determines that the request for designation was materially defective or if we cannot assure sufficient quantity of the applicable medicine to meet the needs of patients with the rare disease or condition, or if a competitor is able to gain approval for the same medicine in a safer or more effective form or that makes a major contribution to patient care. If we lose orphan drug exclusivity on any of our medicines, we may face increased competition and lose market share for such medicine.

Risks Associated with our Businesses as a Whole

Risks related to our financial condition

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

Many of our medicines are undergoing clinical studies or are in the early stages of research and development. Most of our programs will require significant additional research, development, manufacturing, preclinical and clinical testing, marketing authorizations, preclinical activities and commitment of significant additional resources prior to their successful commercialization. In addition, as we commercialize more medicines on our own, we will need to invest significant financial resources to continue developing the infrastructure required to successfully commercialize our medicines, including the expansion of our manufacturing capabilities. All of these activities will require significant cash. As of December 31, 2023, we had cash, cash equivalents and short-term investments equal to $2.3 billion. If we or our partners do not meet our goals to successfully commercialize our medicines, including our commercial medicines, or to license certain medicines and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors such as:

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

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

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

Because drug discovery and development require substantial lead-time and money prior to commercialization, our expenses have generally exceeded our revenue since we were founded in January 1989. As of December 31, 2023, we had an accumulated deficit of approximately $1.8 billion and stockholders' equity of approximately $0.4 billion. Most of our income has historically come from collaborative arrangements, including commercial revenue from royalties and R&D revenue, with additional income from research grants and the sale or licensing of our patents, as well as interest income. We will now and continuing into the foreseeable future need to invest significant financial resources to develop capabilities to commercialize medicines on our own and expect that our income in the future will be driven primarily by commercial sales. If we do not earn substantial revenue from commercial sales, we may incur additional operating losses in the future, which could restrict our ability to successfully develop additional medicines or sustain future profitability.

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

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

Risks related to our intellectual property

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

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

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

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

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

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

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

Risks related to product liability

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

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

Risks related to our personnel

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

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

Risks related to pandemics, climate change and other events

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

Our business could be adversely affected by health epidemics in regions where we or our partners are commercializing our medicines, have concentrations of clinical trial sites or other business operations, and could cause disruption in the operations of third-party manufacturers and contract research organizations upon whom we rely. For example, enrollment in some of our clinical trials was delayed due to the COVID-19 pandemic.

In recent years, extreme weather events and changing weather patterns have become more common. As a result, we are potentially exposed to varying natural disaster or extreme weather risks such as hurricanes, tornadoes, fires, droughts, floods, or other events that may result from the impact of climate change on the environment. The potential impacts of climate change may also include increased operating costs associated with additional regulatory requirements and investments in reducing energy, water use and greenhouse gas emissions. In addition, we currently manufacture most of our research and clinical supplies in a manufacturing facility located in Carlsbad, California. We manufacture the finished drug product for TEGSEDI, WAINUA and WAYLIVRA at third-party contract manufacturers. Biogen manufactures the finished drug product for SPINRAZA and QALSODY. The facilities and the equipment we, our partners and our contract manufacturers use to research, develop and manufacture our medicines would be costly to replace and could require substantial lead time to repair or replace.

Our facilities or those of our partners or contract manufacturers may be harmed by natural disasters or other events outside our control, such as earthquakes, wars, civil or political unrest, deliberate acts of sabotage, terrorism or industrial accidents such as fire and explosion, whether due to human or equipment error, and if such facilities are affected by a disaster or other event, our development and commercialization efforts would be delayed. Although we possess property damage and business interruption insurance coverage, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all. In addition, our development and commercialization activities could be harmed or delayed by a shutdown of the U.S. government, including the FDA.

Risks related to cybersecurity, social media and artificial intelligence

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

We are dependent upon our own and third-party information technology systems, infrastructure and data, including mobile technologies, to operate our business. The multitude and complexity of our computer systems may make them vulnerable to service interruption or destruction, disruption of data integrity, malicious intrusion, or random attacks. Likewise, data privacy or security incidents or breaches by employees or others may pose a risk that sensitive data, including our intellectual property, trade secrets or personal information of our employees, patients, customers or other business partners may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity, particularly as companies (including us) moved to more remote work structures during and following the COVID-19 pandemic. In addition, the number and frequency of cybersecurity events globally may be heightened during times of geopolitical tension or instability between countries, including, for example, the ongoing conflicts in Eastern Europe and the Middle East.

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

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

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

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

Risks related to our securities and the global credit markets

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

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

If the price of our securities continues to be highly volatile, this could make it harder to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding December 31, 2023, the closing market price of our common stock ranged from $52.27 to $32.69 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical study results, technological innovations or new products being developed by us or our competitors, the commercial success of our approved medicines, governmental regulation, marketing authorizations, changes in payers' reimbursement policies, developments in patent or other proprietary rights and public concern regarding the safety of our medicines.

Broad market factors may materially harm the market price of our common stock irrespective of our operating performance. For example, recent events such as the COVID-19 pandemic, the ongoing conflicts in Eastern Europe and the Middle East, and the failure of Silicon Valley Bank have caused disruptions of global financial markets and resulted in increased volatility in the trading price of our common stock. In addition, industry factors may materially harm the market price of our common stock. Nasdaq, and the market for biotechnology companies in particular, have historically experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of the particular companies affected. The trading prices and valuations of these stocks, and of ours, may not be predictable. A loss of investor confidence in the market for biotechnology or pharmaceutical stocks or the stocks of other companies that investors perceive to be similar to us, the opportunities in the biotechnology and pharmaceutical market or the stock market in general, could depress our stock price regardless of our business, prospects, financial conditions or results of operations.

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

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

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

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

In 2023, we completed a $575 million offering of 1.75% Notes and used $488.2 million of the net proceeds from the issuance of the 1.75% Notes to repurchase $504.4 million of our 0.125% Notes. In 2021, we completed a $632.5 million offering of 0% Notes and used a portion of the net proceeds from the issuance of the 0% Notes to repurchase $247.9 million of our 1% Notes for $257.0 million. In 2019, we entered into privately negotiated exchange and/or subscription agreements with certain new investors and certain holders of our existing 1% Notes to exchange $375.6 million of our 1% Notes for $439.3 million of our 0.125% Notes, and to issue $109.5 million of our 0.125% Notes. Additionally, in connection with the pricing of our 0% Notes and 0.125% Notes, we entered into call spread transactions in which we purchased note hedges and sold warrants. Terminating or unwinding the call spread transactions could require us to make substantial payments to the counterparties under those agreements or may increase our stock price. The costs or any increase in stock price that may arise from terminating or unwinding such agreements could make an acquisition of our company significantly more expensive to the purchaser.

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

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

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. For example, as of December 31, 2023, we may issue approximately 28.2 million shares of our common stock upon conversion of our 1.75% Notes, 0% Notes and 0.125% Notes. In connection with the issuance of the 0% Notes and 0.125% Notes, we entered into certain call spread transactions covering 10.9 million shares and 6.6 million shares, respectively, that we expect will offset the dilution to holders of common stock upon any conversion of those notes. In addition, of the shares reserved, 6.1 million shares are reserved for issuance upon conversion of 0.125% Notes that we have repurchased and are currently held by us in treasury (and thus would not be dilutive). As a result, to the extent we elect to convert the 0.125% Notes held by us in treasury, we expect we would receive up to 6.1 million shares upon settlement of related convertible note hedges (without any additional dilution caused by the conversion of the 0.125% Notes held in treasury). However, the anti-dilutive effect of the convertible note hedges is offset by certain warrant transactions we entered into in connection with the issuance of the 0% Notes and the 0.125% Notes. The addition of any of these shares into the public market may have an adverse effect on the price of our securities.

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

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

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

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

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

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

Risks related to compliance with laws

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

Our operations are subject to extensive legal and regulatory requirements affecting the health care industry, including federal and state anti-kickback laws, false claims laws, transparency laws, such as the federal Sunshine Act, and health information privacy and security laws, which are subject to change at any time. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. Penalties for violations of applicable healthcare laws and regulations may include significant civil, criminal and administrative penalties, damages, disgorgement, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and additional reporting requirements and oversight if we enter into a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws. In addition, violations may also result in reputational harm, diminished profits and future earnings.

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

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

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

In such an event, we may be held liable for any resulting damages, and any liability could exceed our resources. Although we carry insurance for pollution liability in amounts and types that we consider commercially reasonable, the coverage or coverage limits of our insurance policies may not be adequate. If our losses exceed our insurance coverage, our financial condition would be adversely affected.

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

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

The SEC and other regulators have continued to adopt new rules and regulations and make additional changes to existing regulations that require our compliance. In July 2010, the Dodd-Frank Wall Street Reform and Protection Act, or the Dodd-Frank Act, was enacted, and in August 2022, the SEC adopted additional rules and regulations under the Dodd-Frank Act related to "say on pay" and proxy access. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which has and may in the future lead to additional compliance costs and impact the manner in which we operate our business.

Risks related to taxes

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

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

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

In addition, under Sections 382 and 383 of the Code, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50 percentage-point cumulative change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change NOL carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our NOL carryforwards or other tax attributes is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. As a result of our merger with Akcea Therapeutics, Inc. in 2020, or the Akcea Merger, we are subject to the separate return limitation year, or SRLY, rules. Under the SRLY rules, our utilization of Akcea's pre-merger NOL and tax credit carryforwards is limited to the amount of income that Akcea contributes to our consolidated taxable income. The Akcea pre-merger tax attributes cannot be used to offset any of the income that Ionis contributes to our consolidated taxable income. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

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

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

We could be subject to additional tax liabilities.

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

Item 1B. Unresolved Staff Comments

Not applicable.

Item 1C. Cybersecurity

Risk management and strategy

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

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

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

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

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

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

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

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

Governance

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

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

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

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

Item 2. Properties

As of February 15, 2024, the following are the primary facilities in which we operate:

Property Description	Location	Square Footage	Owned or Leased	Initial Lease Term End Date	Lease Extension Options
Laboratory and office space facility	Carlsbad, CA	176,300	Leased	2037	Two, five-year options to extend
Office and meeting space facility	Carlsbad, CA	74,000	Leased	2037	Two, five-year options to extend
Manufacturing facility	Carlsbad, CA	26,800	Owned		
Manufacturing support facility	Carlsbad, CA	25,800	Leased	2026	One, five-year option to extend
Office space facility	Boston, MA	14,300	Leased	2029	One, five-year option to extend
Office space facility	Carlsbad, CA	5,800	Leased	2027	None
Warehouse facility	Carlsbad, CA	4,200	Leased	2028	None
Office space facility	Dublin, Ireland	3,900	Leased	2025	None
		331,100			

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

Item 3. Legal Proceedings

For details of legal proceedings, refer to Part IV, Item 15, Note 11, *Legal Proceedings,* in the Notes to the Consolidated Financial Statements.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

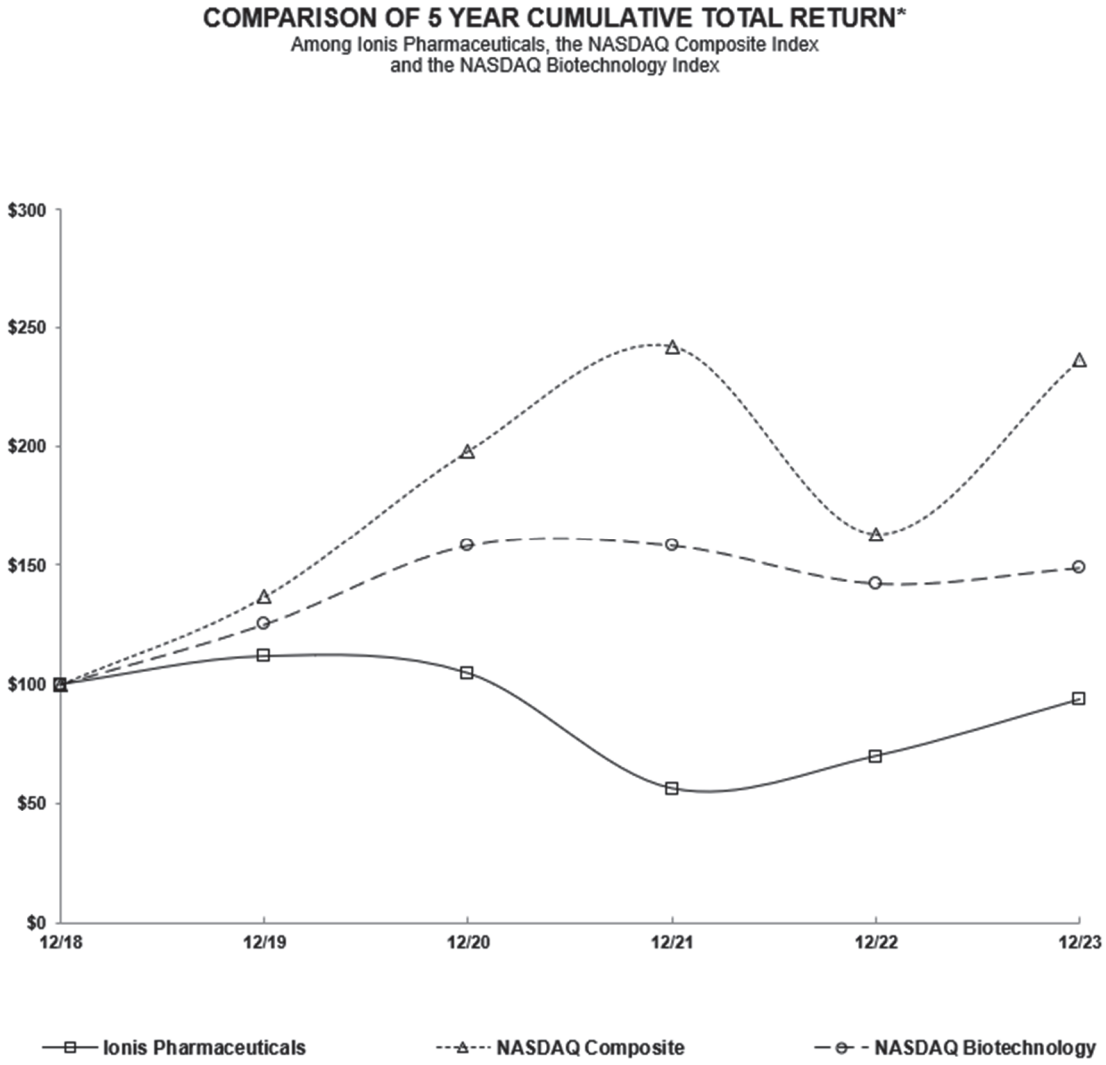
Market Information and Dividends

Our common stock is traded publicly through The Nasdaq Global Select Market under the symbol "IONS." As of February 15, 2024, there were approximately 476 stockholders of record of our common stock. Because many of our shares are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of stockholders represented by these record holders.

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

Performance Graph (1)

Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2018 in our common stock, the Nasdaq Composite Index (total return) and the Nasdaq Biotechnology Index. The total return assumes reinvestment of dividends.



* $100 invested on December 31, 2018 in stock or index, including reinvestment of dividends. Fiscal year ending December 31.

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN
Among Ionis Pharmaceuticals, Inc., the Nasdaq Composite Index,
and the Nasdaq Biotechnology Index

	Dec-18	Dec-19	Dec-20	Dec-21	Dec-22	Dec-23
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 111.75	$ 104.59	$ 56.29	$ 69.87	$ 93.58
Nasdaq Composite Index	$ 100.00	$ 136.69	$ 198.10	$ 242.03	$ 163.28	$ 236.17
Nasdaq Biotechnology Index	$ 100.00	$ 125.11	$ 158.17	$ 158.20	$ 142.19	$ 148.72

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

Item 6. Reserved

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

This financial review presents our operating results for each of the two years in the period ended December 31, 2023, and our financial condition as of December 31, 2023. Refer to our 2022 Form 10-K for our results of operations for 2022 compared to 2021. Except for the historical information contained herein, the following discussion contains forward-looking statements that are subject to known and unknown risks, uncertainties and other factors that may cause our actual results to differ materially from those expressed or implied by such forward-looking statements. We discuss such risks, uncertainties and other factors throughout this report and specifically under Item 1A of Part I of this report, *Risk Factors*. In addition, the following review should be read in conjunction with the information presented in our consolidated financial statements and the related notes to our consolidated financial statements included in Item 8 of Part II of this report.

Overview

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

Results of Operations

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

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

Revenue

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

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

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

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

WAINUA (Eplontersen) Collaboration with AstraZeneca

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

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

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

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

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

Operating Expenses

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

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

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

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

Cost of Sales

Our cost of sales is comprised of costs related to our commercial revenue, which consisted of manufacturing costs, including certain fixed costs, transportation and freight, indirect overhead costs associated with the manufacturing and distribution of TEGSEDI and WAYLIVRA and certain associated period costs.

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

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

Research, Development and Patent Expenses

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

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

	Year Ended December 31,	
	2023	2022
Research, development and patent expenses, excluding non-cash compensation expense related to equity awards	$ 821.7	$ 759.4
Non-cash compensation expense related to equity awards	77.9	73.7
Total research, development and patent expenses	$ 899.6	$ 833.1

Drug Discovery

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

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

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

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

Drug Development

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

	Year Ended December 31,	
	2023	2022
WAINUA	$ 115.5	$ 103.9
TEGSEDI and WAYLIVRA	8.1	10.6
Olezarsen	138.3	68.1
Donidalorsen	24.9	14.1
Zilganersen	8.4	5.6
Ulefnersen	10.8	8.4
Other development projects	101.0	123.5
Development overhead expenses	123.3	92.0
Total drug development, excluding non-cash compensation expense related to equity awards	530.3	426.2
Non-cash compensation expense related to equity awards	34.5	31.5
Total drug development expenses	$ 564.8	$ 457.7

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

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

Medical Affairs

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

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

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

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

Manufacturing and Development Chemistry

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

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

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

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

R&D Support

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

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

	Year Ended December 31,	
	2023	2022
Personnel costs	$ 27.2	$ 21.2
Occupancy	28.7	19.2
Consulting	4.8	0.8
Patent expenses	4.3	4.7
Insurance	3.6	3.8
Computer software and licenses	2.7	1.9
Other	9.7	8.2
Total R&D support expenses, excluding non-cash compensation expense related to equity awards	81.0	59.8
Non-cash compensation expense related to equity awards	15.0	14.1
Total R&D support expenses	$ 96.0	$ 73.9

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

Selling, General and Administrative Expenses

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

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

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

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

Investment Income

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

Interest Expense

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

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

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

Interest Expense Related to Sale of Future Royalties

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

Loss on Investments

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

Gain on Sale of Real Estate

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

Other Income (Expense)

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

Income Tax Expense (Benefit)

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

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

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

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

Net Loss and Net Loss per Share

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

Liquidity and Capital Resources

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

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

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

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

Our contractual obligations consist primarily of our convertible debt. In addition, we also have a facility mortgage, facility leases, equipment financing arrangements and other obligations. We believe our cash, cash equivalents and short-term investments, as well as plans for cash in the future, will be sufficient to fund our planned operations and these obligations. We have not entered into, nor do we currently have, any off-balance sheet arrangements (as defined under SEC rules).

Convertible Debt and Call Spread

Refer to our Convertible Debt and Call Spread accounting policies in Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, and Note 7, *Long-Term Obligations and Commitments*, in the Notes to the Consolidated Financial Statements for the significant terms of each convertible debt instrument.

Operating Facilities

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

Operating Leases

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

Royalty Revenue Monetization

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

Other Obligations

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2023 for the purchase of services, capital equipment and materials as part of our normal course of business.

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

Critical Accounting Estimates

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the U.S. As such, we make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management reviews the development, selection and disclosure of such estimates with the audit committee of our board of directors. In the following paragraphs, we describe the specific risks associated with these critical accounting estimates and we caution that future events rarely develop exactly as one may expect, and that best estimates may require adjustment. Our significant accounting policies are outlined in Part IV, Item 15, Note 1, *Organization and Significant Accounting Policies*, in the Notes to the Consolidated Financial Statements.

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

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

The following are descriptions of our critical accounting estimates.

Revenue Recognition

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

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

Research and development revenue under collaborative agreements

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

- Identifying the performance obligations contained in the agreement

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

- Determining the transaction price, including any variable consideration

  To determine the transaction price, we review the amount of consideration we are eligible to earn under the agreement. We do not typically include any payments we may receive in the future in our initial transaction price since the payments are typically not probable because they are contingent upon certain future events. We reassess the total transaction price at each reporting period to determine if we should include additional payments in the transaction price that have become probable.

- Allocating the transaction price to each of our performance obligations

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

The R&D revenue we recognize each period is comprised of several types of revenue, including amortization from upfront payments, milestone payments, license fees and other services that are recognized immediately or amortized over the period in which we satisfy our performance obligation. Each of these types of revenue require us to make various judgements and estimates.

R&D Services with Upfront Payments

We recognize revenue from the amortization of upfront payments as we perform R&D services. We use an input method to estimate the amount of revenue to recognize each period. This method requires us to make estimates of the total costs we expect to incur to complete our R&D services performance obligation or the total amount of effort it will take us to complete our R&D services performance obligation. If we change our estimates, we may have to adjust our revenue.

Milestone Payments

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

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

License Fees

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

Estimated Liability for Clinical Development Costs

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

As of December 31, 2023, a hypothetical 10 percent increase in our liability for preclinical and clinical development costs would have resulted in an increase in our loss before income tax benefit and accrued liabilities of approximately $10.6 million.

Liability Related to Sale of Future Royalties

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

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

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Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are exposed to changes in interest rates primarily from our investments in certain short-term investments. We primarily invest our excess cash in highly liquid short-term investments of the U.S. Treasury and reputable financial institutions, corporations, and U.S. government agencies with strong credit ratings. We typically hold our investments for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we were not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments as of December 31, 2023 and will not be subject to any material risks arising from these changes in the foreseeable future.

Item 8. Financial Statements and Supplementary Data

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

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

None.

Item 9A. Controls and Procedures

Disclosure Controls and Procedures

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

As of the end of the period covered by this report on Form 10-K, we carried out an evaluation of our disclosure controls and procedures under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on our evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2023.

Management's Report on Internal Control over Financial Reporting

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

As of December 31, 2023, we assessed the effectiveness of our internal control over financial reporting based on the criteria for effective internal control over financial reporting under the 2013 "Internal Control—Integrated Framework," issued by the Committee of Sponsoring Organizations, or COSO, of the Treadway Commission, under the supervision of, and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer. Based on that assessment, our management concluded that we maintained effective internal control over financial reporting as of December 31, 2023.

Ernst & Young LLP, an independent registered public accounting firm, audited the effectiveness of our internal control over financial reporting as of December 31, 2023, as stated in their attestation report, which is included elsewhere herein.

Changes in Internal Control over Financial Reporting

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

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on Internal Control over Financial Reporting

We have audited Ionis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2023, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Ionis Pharmaceuticals, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2023, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2023 and 2022, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2023, and the related notes and our report dated February 21, 2024 expressed an unqualified opinion thereon.

Basis for Opinion

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

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

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

Definition and Limitations of Internal Control Over Financial Reporting

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

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

/s/ Ernst & Young LLP

San Diego, California
February 21, 2024

Item 9B. Other Information

Trading Plans

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

* Contract, instruction or written plan intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) under the Exchange Act.

** "Non-Rule 10b5-1 trading arrangement" as defined in item 408(c) of Regulation S-K under the Exchange Act.

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

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

We incorporate by reference the information required by this Item with respect to directors and the Audit Committee from the information under the caption "ELECTION OF DIRECTORS," including in particular the information under "Nominating, Governance and Review Committee" and "Audit Committee," contained in our definitive Proxy Statement, which we will file with the Securities and Exchange Commission within 120 days after the end of the fiscal year ended December 31, 2023, or the Proxy Statement.

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

We incorporate by reference the required information concerning our Code of Ethics from the information under the caption "Code of Ethics and Business Conduct" contained in the Proxy Statement. Our Code of Ethics and Business Conduct is posted on our website at www.ionispharma.com[(1)]. We intend to make all required disclosures regarding any amendments to, or waivers from, provisions of our Code of Ethics and Business conduct on our website.

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

Delinquent Section 16(a) Reports

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

Item 11. Executive Compensation

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

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

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

Securities Authorized for Issuance under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2023.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders (a)	14,090,732	$ 48.43	9,976,286(b)
Total	14,090,732	$ 48.43	9,976,286

(a) Consists of five Ionis plans: 1989 Stock Option Plan, Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, 2011 Equity Incentive Plan, 2020 Equity Incentive Plan and Employee Stock Purchase Plan, or ESPP.
(b) Of these shares, 386,792 were available for purchase under the ESPP as of December 31, 2023.

For additional details about our equity compensation plans, including a description of each plan, refer to Part IV, Item 15, Note 8, *Stockholders' Equity*, in the Notes to the Consolidated Financial Statements.

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

We incorporate by reference the information required by this item to the information under the captions "Information Regarding the Board and Corporate Governance" and "Certain Relationships and Related Transactions" contained in the Proxy Statement.

Item 14. Principal Accountant Fees and Services

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

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a)(1) Index to Financial Statements

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

(a)(2) Index to Financial Statement Schedules

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

(a)(3) Index to Exhibits

INDEX TO EXHIBITS

Exhibit Number	Description of Document
2.1	Agreement and Plan of Merger, dated as of August 30, 2020, among Akcea Therapeutics, Inc., Ionis Pharmaceuticals, Inc. and Avalanche Merger Sub, Inc., filed as an exhibit to the Registrant's Current Report on Form 8-K filed August 31, 2020 and incorporated herein by reference.
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
3.2	Certificate of Amendment to Restated Certificate of Incorporation, filed as an exhibit to the Registrant's Notice of Annual Meeting and Proxy Statement, for the 2014 Annual Meeting of Stockholders, filed on April 25, 2014 and incorporated herein by reference.
3.3	Certificate of Amendment to Restated Certificate of Incorporation, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 18, 2015 and incorporated herein by reference.
3.4	Amended and Restated Bylaws, filed as an exhibit to the Registrant's Current Report on Form 8-K filed March 29, 2021 and incorporated herein by reference.
4.1	Description of the Registrant's Securities, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference.
4.2	Certificate of Designation of the Series C Junior Participating Preferred Stock, filed as an exhibit to Registrant's Current Report on Form 8-K filed December 13, 2000 and incorporated herein by reference.
4.3	Specimen Common Stock Certificate, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
4.4	Indenture, dated as of December 19, 2019, by and between the Registrant and U.S. Bank National Association, as trustee, including Form of 0.125 percent Convertible Senior Note due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 23, 2019 and incorporated herein by reference.
4.5	Form of Exchange and/or Subscription Agreement for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.6	Form of Convertible Note Hedge Transactions Confirmation for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.7	Form of Warrant Transactions Confirmation for Convertible Senior Notes due 2024, filed as an exhibit to the Registrant's Current Report on Form 8-K filed December 12, 2019 and incorporated herein by reference.
4.8	Indenture, dated as of April 12, 2021, by and between the Registrant and U.S. Bank National Association, as trustee, including Form of 0 percent Convertible Senior Note due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.
4.9	Form of Warrant Confirmation for Convertible Senior Notes due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.
4.10	Form of Convertible Note Hedge Confirmation for Convertible Senior Notes due 2026, filed as an exhibit to the Registrant's Current Report on Form 8-K filed April 13, 2021 and incorporated herein by reference.
4.11	Indenture, dated as of June 12, 2023, by and between the Registrant and U.S. Bank Trust Company, a National Association, as trustee, including Form of 1.75 percent Global Note due in 2028, filed as an exhibit to the Registrant's Current Report on Form 8-K filed June 12, 2023 and incorporated herein by reference.
10.1*	Second Amended Non-Employee Director Compensation Policy, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 and incorporated herein by reference.
10.2*	Registrant's Amended and Restated Severance Benefit Plan dated March 17, 2022, filed as an exhibit to the Registrant's Quarterly Report on form 10-Q for the quarter ended March 31, 2022 and incorporated herein by reference.
10.3	Form of Indemnity Agreement entered into between the Registrant and its Directors and Executive Officers with related schedule
10.4	Form of Employee Confidential Information and Inventions Agreement, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference.
10.5*	Registrant's Amended and Restated 2000 Employee Stock Purchase Plan, filed as an exhibit to Registrant's Current Report on Form 8-K filed on March 26, 2019 and incorporated herein by reference.
10.6*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 and incorporated herein by reference.
10.7*	Form of Option Agreement for Options granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.

10.8*	Forms of Restricted Stock Unit Grant Notice and Restricted Stock Unit Agreement for Restricted Stock Units granted under the Ionis Pharmaceuticals, Inc. Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 and incorporated herein by reference.
10.9*	Amended and Restated Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Notice of 2021 Annual Meeting of Stockholders and Proxy Statement filed on April 23, 2021 and incorporated herein by reference.
10.10*	Form of Option Agreement under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.
10.11*	Form of Time-Vested Restricted Stock Unit Agreement for Restricted Stock Units granted under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.
10.12*	Forms of Performance Based Restricted Stock Unit Grant Notice and Performance Based Restricted Stock Unit Agreement for Performance Based Restricted Stock Units granted prior to January 1, 2023 under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference.
10.13*	Forms of Performance Based Restricted Stock Unit Grant Notice and Performance Based Restricted Stock Unit Agreement for Performance Based Restricted Stock Units granted beginning January 1, 2023 under the 2011 Equity Incentive Plan, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.
10.14*	Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.15*	Form of Global Option Agreement for options granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.16*	Form of Global Restricted Stock Unit Agreement for restricted stock units granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.17*	Forms of Restricted Stock Unit Grant Notice, Stock Option Grant Notice and Stock Option Exercise Notice for options granted under the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, filed as an exhibit to the Registrant's Registration Statement on Form S-8 filed on December 31, 2020 and incorporated herein by reference.
10.18	Loan Agreement between Ionis Faraday, LLC and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.19	Guaranty between the Registrant and UBS AG dated July 18, 2017, filed as an exhibit to the Registrant's Current Report on Form 8-K filed July 21, 2017 and incorporated herein by reference.
10.20	Purchase and Sale Agreement between Ionis Gazelle, LLC and 2850 2855 & 2859 Gazelle Owner (DE) LLC dated as of October 20, 2022, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.21	Purchase and Sale Agreement between the Registrant and Oxford I Asset Management USA Inc. dated as of October 20, 2022, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.22	First Amendment dated June 15, 2023 to the Purchase and Sale Agreement by and between the Registrant and Oxford I Asset Management USA Inc. dated as of October 20, 2022, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2023 and incorporated herein by reference.
10.23	Lease Agreement dated October 20, 2022 between the Registrant and 2850 2855 & 2859 Gazelle Owner (DE) LLC, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.24	Amended and Restated Lease Agreement between the Registrant and Lots 21 & 22 Owner (DE) LLC dated as of August 21, 2023, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.

10.25	First Amendment dated as of November 6, 2023 to Amended and Restated Lease Agreement between the Registrant and Lots 21 & 22 Owner (DE) LLC dated as of August 21, 2023.
10.26	Defeasance Pledge and Security Agreement dated as of October 20, 2022 by and among Ionis Gazelle, LLC, Wells Fargo Bank, National Association, as Trustee for the Benefit of the Registered Holders of UBS Commercial Mortgage Trust 2017-C3, Commercial Mortgage Pass-Through Certificates, Series 2017-C3, and U.S. Bank Trust Company, National Association, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.27	Defeasance Assignment, Assumption and Release Agreement dated as of October 20, 2022 by and among Ionis Gazelle, LLC, DHC UBSCM 17 C3 Successor Borrower-R, LLC, Wells Fargo Bank, National Association, as Trustee for the Benefit of the Registered Holders of UBS Commercial Mortgage Trust 2017-C3, Commercial Mortgage Pass-Through Certificates, Series 2017-C3, Midland Loan Services, a division of PNC Bank, National Association, and U.S. Bank Trust Company, National Association, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference.
10.28	Defeasance Account Agreement dated as of October 20, 2022 by and among Ionis Gazelle, LLC, U.S. Bank Trust Company, National Association, U.S. Bank National Association, as Trustee for the Benefit of the Registered Holders of UBS Commercial Mortgage Trust 2017-C3, Commercial Mortgage Pass-Through Certificates, Series 2017-C3, and Midland Loan Services, a division of PNC Bank, National Association, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.29	Exclusive License Agreement between the Registrant and the University of Massachusetts dated January 14, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.30	Research, Development and License Agreement between the Registrant and Glaxo Group Limited dated March 30, 2010, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2010 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.31	Amendment #1 to the Research, Development and License Agreement dated May 11, 2011 by and between the Registrant and Glaxo Group Limited, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2011 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.32	Amendment #2 to the Research, Development and License Agreement by and between the Registrant and Glaxo Group Limited dated October 30, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.33	Amendment No. 3 to the Research, Development and License Agreement by and between the Registrant and Glaxo Group Limited dated July 10, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.34	Amendment #4 to the Research, Development and License Agreement by and between the Registrant and Glaxo Group Limited dated April 10, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.35	Amendment #5 to the Research, Development and License Agreement by and between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated June 27, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.36	Amendment #6 to Research, Development and License Agreement by and between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated September 2, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.37	Amendment #7 to the Research, Development and License Agreement by and between the Registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Limited dated March 4, 2016, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.38	Amendment #8 to the Research, Development and License Agreement by and between the Registrant, Glaxo Group Limited and Glaxosmithkline Intellectual Property Development Limited, dated July 29, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.39	Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated October 26, 2011, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.40	Amendment to Amended and Restated Collaboration and License Agreement between the Registrant and Cold Spring Harbor Laboratory dated March 14, 2014, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.41	Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated January 3, 2012, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.42	Amendment #1 to the Development, Option and License Agreement between the Registrant and Biogen Idec International Holding Ltd. dated December 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.43	Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated December 7, 2012, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2012 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.44	Amendment #1 to Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated August 13, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2013 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.45	Amendment No.2 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated October 15, 2014, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2014 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.46	Amendment No.3 to the Collaboration, License and Development Agreement between the Registrant and AstraZeneca AB dated January 18, 2016, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.47	Amendment No. 4 to the Collaboration, License and Development Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.48	HTT Research, Development, Option and License Agreement among the Registrant, F. Hoffmann-La Roche Ltd and Hoffman-La Roche Inc. dated April 8, 2013, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.49	Amendment #1 to HTT Research, Development, Option and License Agreement between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. dated January 9, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.50	Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated January 8, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.51	Amendment Number One to the Second Amended and Restated Strategic Collaboration and License Agreement between the Registrant and Alnylam Pharmaceuticals, Inc. dated July 13, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.52	Strategic Collaboration Agreement between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2015 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.53	Amendment No. 1 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB, dated October 18, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.54	Amendment No. 2 dated April 30, 2020 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) is the type that the Registrant treats as private or confidential.
10.55	Amendment No. 3 dated December 17, 2020 to the Strategic Collaboration Agreement by and between the Registrant and AstraZeneca AB dated July 31, 2015, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.56	Strategic Collaboration, Option and License Agreement by and among Akcea Therapeutics, Inc. and Novartis Pharma AG, dated January 5, 2017, filed as an exhibit to Akcea Therapeutics, Inc.'s Form S-1 filed March 27, 2017 and incorporated herein by reference.
10.57	Amendment No. 1 to the Strategic Collaboration, Option and License Agreement between Akcea Therapeutics, Inc. and Novartis Pharma AG dated February 22, 2019, filed as an exhibit to Akcea Therapeutics, Inc.'s Quarterly Report on Form 10-Q for the quarter ended March 30, 2019 and incorporated herein by reference.
10.58	Stock Purchase Agreement among the Registrant, Akcea Therapeutics, Inc. and Novartis Pharma AG dated January 5, 2017, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 and incorporated herein by reference.
10.59	Research Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc. dated December 19, 2017, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2017 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.60	New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated April 19, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.61	Amendment No. 1 to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement between the Registrant and Biogen MA Inc., dated August 16, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.62	Side Letter dated December 31, 2020 to the New Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated April 19, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.63	Factor B Development Collaboration, Option and License Agreement by and between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., dated October 9, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.

10.64	First Amendment dated July 8, 2022 to Factor B Development, Collaboration, Option and License Agreement by and between the Registrant, F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., dated October 9, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2022. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.65	Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated October 17, 2018, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2018 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.66	Letter Agreement between the Registrant and Biogen MA Inc. dated October 28, 2016, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2016 and incorporated herein by reference. Portions of this exhibit have been omitted and separately filed with the SEC with a request for confidential treatment.
10.67	Amendment No. 1 to Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc., dated May 2, 2019, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2019 and incorporated herein by reference.
10.68	Collaboration and License Agreement by and between the Registrant and Novartis Pharma AG dated as of August 2, 2023, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.69	Research, Development, and License Agreement by and among the Registrant, F. Hoffmann-La Roche Ltd., and Hoffmann-La Roche Inc. dated as of September 26, 2023, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.70	Side Letter dated June 11, 2020 to the Second Amended and Restated Strategic Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated October 17, 2018, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.71	Collaboration and License Agreement by and between the Registrant and BicycleTX Limited dated July 9, 2021, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.72	Amendment No. 1 dated December 17, 2021 to the Collaboration and License Agreement by and between the Registrant and BicycleTX Limited dated July 9, 2021, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.73	Amendment No. 2 dated July 28, 2022 to the Collaboration and License Agreement by and between the Registrant and BicycleTx Limited dated July 9, 2021, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.74	Amendment No. 3 dated April 27, 2023 to the Collaboration and License Agreement by and between the Registrant and BicycleTx Limited dated July 9, 2021, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.75	Amended and Restated Neurology Drug Discovery and Development Collaboration, Option and License Agreement by and between the Registrant and Biogen MA Inc. dated July 12, 2021, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.76	Collaboration and License Agreement by and between Akcea Therapeutics, Inc. and AstraZeneca AB dated December 6, 2021, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.

10.77	Letter Agreement dated June 29, 2023 in reference to the Collaboration and License Agreement dated December 6, 2021 by and between Akcea Therapeutics, Inc. and AstraZeneca AB, filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2023 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.78	Collaboration and License Agreement between the Registrant and Metagenomi, Inc. dated November 10, 2022, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.79	Royalty Purchase Agreement by and between the Registrant, Akcea Therapeutics, Inc. and Royalty Pharma Investments 2019 ICAV dated as of January 9, 2023, filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2022 and incorporated herein by reference. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
10.80	License Agreement by and between the Registrant and Otsuka Pharmaceuticals Co., LTD. dated as of December 15, 2023. Portions of this exhibit have been omitted because they are both (i) not material and (ii) the type that the Registrant treats as private or confidential.
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney – Included on the signature page of this Annual Report on Form 10-K.
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1+	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
97	Registrant's Amended and Restated Clawback Policy
101	The following financial statements from the Ionis Pharmaceuticals, Inc. Annual Report on Form 10-K for the year ended December 31, 2023, formatted in Extensive Business Reporting Language (XBRL): (i) consolidated balance sheets, (ii) consolidated statements of operations, (iii) consolidated statements of comprehensive income (loss), (iv) consolidated statements of stockholders' equity (v) consolidated statements of cash flows, and (vi) notes to consolidated financial statements (detail tagged).
104	Cover Page Interactive Data File (formatted in iXBRL and included in exhibit 101).

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

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

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 21st day of February, 2024.

IONIS PHARMACEUTICALS, INC.

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

POWER OF ATTORNEY

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

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

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

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IONIS PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Ionis Pharmaceuticals, Inc. (the Company) as of December 31, 2023 and 2022, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2023, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2023 and 2022, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2023, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2023, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), and our report dated February 21, 2024 expressed an unqualified opinion thereon.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matters

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

Estimated Liability for Clinical Development Costs

Description of the Matter

As of December 31, 2023, the Company accrued $106 million for clinical development expenses. As discussed in Note 1 to the consolidated financial statements, the Company records costs for clinical trial activities based upon estimates of costs incurred through the balance sheet date that have yet to be invoiced related to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. The Company estimates its liability using assumptions about study and patient activities and the related expected expenses for those activities based on the contracted fees with service providers.

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

How We Addressed the Matter in Our Audit

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

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

Accounting for the Royalty Pharma Sale of Future Royalties Transaction

Description of the Matter

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

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

How We Addressed the Matter in Our Audit

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

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

/s/ Ernst & Young LLP

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

San Diego, California
February 21, 2024

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

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

See accompanying notes.

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

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

See accompanying notes.

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

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

See accompanying notes.

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

Description	Common Stock Shares	Common Stock Amount	Additional Paid in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Ionis Stockholders' Equity
Balance at December 31, 2020	140,366	$ 140	$ 1,895,519	$ (21,071)	$ (1,131,306)	$ 743,282
Net loss	—	—	—	—	(28,597)	(28,597)
Change in unrealized losses, net of tax	—	—	—	(11,486)	—	(11,486)
Foreign currency translation	—	—	—	(111)	—	(111)
Issuance of common stock in connection with employee stock plans	1,132	1	11,563	—	—	11,564
Issuance of warrants	—	—	89,752	—	—	89,752
Purchase of note hedges	—	—	(136,620)	—	—	(136,620)
Stock-based compensation expense	—	—	120,678	—	—	120,678
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(288)	—	(16,725)	—	—	(16,725)
Balance at December 31, 2021	141,210	$ 141	$ 1,964,167	$ (32,668)	$ (1,159,903)	$ 771,737
Net loss	—	—	—	—	(269,722)	(269,722)
Change in unrealized losses, net of tax	—	—	—	(24,395)	—	(24,395)
Foreign currency translation	—	—	—	(417)	—	(417)
Issuance of common stock in connection with employee stock plans	1,194	1	6,372	—	—	6,373
Stock-based compensation expense	—	—	100,264	—	—	100,264
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	(346)	—	(10,953)	—	—	(10,953)
Balance at December 31, 2022	142,058	$ 142	$ 2,059,850	$ (57,480)	$ (1,429,625)	$ 572,887
Net loss	—	—	—	—	(366,286)	(366,286)
Change in unrealized gains, net of tax	—	—	—	24,484	—	24,484
Foreign currency translation	—	—	—	351	—	351
Issuance of common stock in connection with employee stock plans	2,283	2	49,439	—	—	49,441
Stock-based compensation expense	—	—	105,809	—	—	105,809
Balance at December 31, 2023	144,341	$ 144	$ 2,215,098	$ (32,645)	$ (1,795,911)	$ 386,686

See accompanying notes.

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

	Year Ended December 31,		
	2023	**2022**	**2021**
Operating activities:			
Net loss	$ (366,286)	$ (269,722)	$ (28,597)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	10,292	14,328	15,487
Amortization of right-of-use operating lease assets	9,647	5,362	1,721
Amortization of other assets	2,559	2,415	2,352
Amortization of premium (discount) on investments, net	(28,885)	7,389	17,776
Amortization of debt issuance costs	6,330	5,373	4,958
Non-cash royalty revenue related to sale of royalties	(44,628)	—	—
Non-cash interest related to sale of future royalties	68,238	—	—
Stock-based compensation expense	105,809	100,264	120,678
Loss (gain) on early retirement of debt	(13,389)	—	8,627
Non-cash losses related to disposal of property, plant and equipment	16,649	531	—
Loss (gain) on sale of real estate assets	161	(150,135)	—
Loss (gain) on investments	1,589	224	(1,092)
Non-cash losses related to other assets	1,661	2,030	2,707
Changes in operating assets and liabilities:			
Contracts receivable	(72,059)	36,358	14,308
Inventories	(6,392)	2,773	(2,841)
Other current and long-term assets	(29,840)	(24,682)	(877)
Accounts payable	8,119	1,094	(6,000)
Income taxes	(4,098)	6,213	(280)
Accrued compensation	18,549	10,368	(26,918)
Accrued liabilities and other current liabilities	(5,506)	46,695	(8,381)
Deferred contract revenue	13,967	(71,248)	(82,829)
Net cash provided by (used in) operating activities	(307,513)	(274,370)	30,799
Investing activities:			
Purchases of short-term investments	(1,770,814)	(1,485,772)	(1,124,193)
Proceeds from sale of short-term investments	1,584,676	989,152	1,344,185
Purchases of property, plant and equipment	(23,805)	(15,721)	(11,955)
Proceeds from sale of real estate assets	22	254,083	—
Acquisition of licenses and other assets, net	(4,206)	(4,378)	(5,946)
Purchases of strategic investments	—	—	(7,185)
Net cash provided by (used in) investing activities	(214,127)	(262,636)	194,906
Financing activities:			
Proceeds from equity, net	49,442	6,373	11,565
Payments of tax withholdings related to vesting of employee stock awards and exercise of employee stock options	—	(10,953)	(16,725)
Proceeds from issuance of 1.75 percent convertible senior notes	575,000	—	—
1.75 percent convertible senior notes issuance costs	(14,175)	—	—
Repurchase of $504.4 million principal amount of 0.125 percent convertible senior notes	(487,943)	—	—
Proceeds from sale of future royalties	500,000	—	—
Payments of transaction costs related to sale of future royalties	(10,434)	(29)	—
Proceeds from real estate transaction	32,352	—	—
Proceeds from the issuance of 0 percent convertible senior notes	—	—	632,500
0 percent convertible senior notes issuance costs	—	—	(15,609)
Repurchase of $247.9 million principal amount of 1 percent convertible senior notes	—	—	(256,963)
Repayment of remaining principal amount of 1 percent convertible senior notes at maturity	—	—	(61,967)
Proceeds from issuance of warrants	—	—	89,752

Purchase of note hedges	—	—	(136,620)
Principal payments on debt	(160)	(50,686)	—
Net cash provided by (used in) financing activities	644,082	(55,295)	245,933
Effects of exchange rates on cash	352	(418)	(111)
Net increase (decrease) in cash and cash equivalents	122,794	(592,719)	471,527
Cash and cash equivalents at beginning of year	276,472	869,191	397,664
Cash and cash equivalents at end of year	$ 399,266	$ 276,472	$ 869,191
Supplemental disclosures of cash flow information:			
Interest paid	$ 6,512	$ 2,898	$ 4,778
Income taxes paid	$ 48,334	$ 5,010	$ 38
Supplemental disclosures of non-cash investing and financing activities:			
Right-of-use assets obtained in exchange for lease liabilities	$ —	$ 168,931	$ 6,641
Amounts accrued for capital and patent expenditures	$ 172	$ 4,767	$ 705

See accompanying notes.

1. Organization and Significant Accounting Policies

Basis of Presentation

In our consolidated financial statements we included the accounts of Ionis Pharmaceuticals, Inc. and the consolidated results of our wholly owned subsidiary, Akcea Therapeutics, Inc. and its wholly owned subsidiaries ("we", "us" or "our").

Organization and Business Activity

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

Use of Estimates

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

Revenue Recognition

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

At contract inception, we analyze our collaboration arrangements to assess whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities and therefore within the scope of ASC Topic 808, *Collaborative Arrangements*, or ASC 808. ASC 808 does not address the recognition and measurement of collaborative arrangements and instead refers companies to use other authoritative accounting literature. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration reflect a vendor-customer relationship and therefore are within the scope of ASC 606, *Revenue from Contracts with Customers*. When we determine elements of a collaboration do not reflect a vendor-customer relationship, we consistently apply the reasonable and rational policy election we made by analogizing to authoritative accounting literature.

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

Steps to Recognize Revenue

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

1. Identify the contract

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

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

2. Identify the performance obligations

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

We may enter into a collaboration agreement in which we provide our partner with an option to license a medicine in the future. We may also provide our partner with an option to request that we provide additional goods or services in the future, such as active pharmaceutical ingredient, or API. We evaluate whether these options are material rights at the inception of the agreement. If we determine an option is a material right, we will consider the option a separate performance obligation. When a partner exercises its option to license a medicine that was not previously determined to be a material right at the inception of the agreement or requests additional goods or services, then we identify a new performance obligation for that item.

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

3. Determine the transaction price

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

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

4. Allocate the transaction price

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

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

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

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

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

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

5. Recognize revenue

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

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

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

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

Amendments to Agreements

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

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

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

Multiple agreements

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

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

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

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

Contracts Receivable

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

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

Unbilled SPINRAZA Royalties

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

Deferred Revenue

We are often entitled to bill our customers and receive payment from our customers in advance of our obligation to provide services or transfer goods to our partners. In these instances, we include the amounts in deferred revenue in our consolidated balance sheets. During the years ended December 31, 2023 and 2022, we recognized $78.2 million and $73.5 million of revenue from amounts that were in our beginning deferred revenue balance for each respective period. For further discussion, refer to our revenue recognition policy above.

Cost of Sales

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

Research, Development and Patent Expenses

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

Income Taxes

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

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

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

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

Basic and Diluted Net Loss per Share

Basic net loss per share

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

Diluted net loss per share

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

- 0 percent convertible senior notes, or 0% Notes;
- Note hedges related to the 0% Notes;
- 0.125 percent convertible senior notes, or 0.125% Notes;
- Note hedges related to the 0.125% Notes;
- Dilutive stock options;
- Unvested restricted stock units, or RSUs;
- Unvested performance restricted stock units, or PRSUs; and
- Employee Stock Purchase Plan, or ESPP.

For the year ended December 31, 2023, common stock underlying the 1.75 percent convertible senior notes, or 1.75% Notes, would also have had an anti-dilutive effect on net loss per share.

Additionally as of December 31, 2023, 2022 and 2021, we had warrants related to our 0% Notes and 0.125% Notes outstanding. We will include the shares issuable under these warrants in our calculation of diluted earnings per share when the average market price per share of our common stock for the reporting period exceeds the strike price of the warrants.

Stock-Based Compensation Expense

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

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

Stock Options and Stock Purchase Rights:

We use the Black-Scholes model to estimate the fair value of stock options granted and stock purchase rights under our ESPP. On the grant date, we use our stock price and assumptions regarding a number of variables to determine the estimated fair value of stock-based payment awards. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. The expected term of stock options granted represents the period of time that we expect them to be outstanding. Historically, we estimated the expected term of options granted based on historical exercise patterns. In 2021, our Compensation Committee approved an amendment to the 2011 Equity Incentive Plan, or 2011 Plan, and the 2020 Equity Incentive Plan, or 2020 Plan, that increased the contractual term of stock options granted under these plans from seven years to ten years for stock options granted on January 1, 2022 and thereafter. We determined that we are unable to rely on our historical exercise data as a basis for estimating the expected life of stock options granted to employees following this change because the contractual term changed and we have no other means to reasonably estimate future exercise behavior. We therefore used the simplified method for determining the expected life of stock options granted to employees in the years ended December 31, 2023 and 2022. Under the simplified method, we calculate the expected term as the average of the time-to-vesting and the contractual life of the options. As we gain additional historical information, we will transition to calculating our expected term based on our historical exercise patterns.

RSU's:

The fair value of RSUs is based on the market price of our common stock on the date of grant. The RSUs we have granted to employees vest annually over a four-year period. The RSUs we granted to our board of directors prior to June 2020 vest annually over a four-year period. RSUs we granted to our board of directors after June 2020 fully vest after one year.

PRSU's:

Beginning in 2020, we added PRSU awards to the compensation for our Chief Executive Officer, Dr. Brett Monia. Beginning in 2022, we added PRSU awards to the compensation for our other Section 16 officers. Under the terms of the PRSUs we granted in 2020 through 2022, one third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (i.e., the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on our relative total shareholder return, or TSR, as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. Under the terms of the grants no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150 percent of the target number depending on our relative TSR. These PRSU awards also included an alternative three-year payout mechanism, or the Alternative Calculation, under which we must calculate an alternative payout at the end of the final three-year measurement period assuming the only measurement period for all shares under the award was the three-year period. If the Alternative Calculation is greater than payouts under the sum of the three years, then such PRSU award will pay out to achieve the number of shares payable under the Alternative Calculation.

Under the terms of the PRSUs we granted in 2023, 100 percent of the PRSUs may vest at the end of the three-year performance period based on our relative TSR as compared to a peer group of companies and as measured at the end of the performance period. Under the terms of the grants, no number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 200 percent of the target number depending on our relative TSR.

We determined the fair value of the PRSUs using a Monte Carlo model because the performance target is based on our relative TSR, which represents a market condition. We are recognizing the grant date fair value of these awards as stock-based compensation expense using the accelerated multiple-option approach over the vesting period.

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

Concentration of Credit Risk

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

Fair Value Measurements

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

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

Cash, Cash Equivalents and Investments

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

We also have equity investments of less than 20 percent ownership in public and private biotechnology companies that we received as part of a technology license or partner agreement. At December 31, 2023, we held equity investments in three publicly traded companies and seven privately held companies.

We are required to measure and record our equity investments at fair value and to recognize the changes in fair value in our consolidated statements of operations. We account for our equity investments in publicly traded companies at their listed stock price. We account for our equity investments in privately held companies at their cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer.

Inventories

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

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

Property, Plant and Equipment

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

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

We depreciate our leasehold improvements using the shorter of the estimated useful life or remaining lease term. We evaluate long-lived assets, which include property, plant and equipment, for impairment on at least a quarterly basis and whenever events or changes in circumstances indicate that we may not be able to recover the carrying amount of such assets.

Accrued Liabilities

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

Convertible Debt

We account for each of our convertible debt instruments as a single unit of accounting, a liability, because we concluded that the conversion features do not require bifurcation as a derivative under ASC 815-15 and we did not issue our convertible debt instruments at a substantial premium. We record debt issuance costs as contra-liabilities in our consolidated balance sheets at issuance and amortize them over the contractual term of the convertible debt instrument using the effective interest rate. The balances of our convertible senior notes presented in our consolidated balance sheets represent the principal balance of each convertible debt instrument less debt issuance costs.

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

Call Spread

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

Liability Related to Sale of Future Royalties

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

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

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

Leases

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

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

Segment Information

We operate as a single segment, Ionis operations, because our chief decision maker reviews operating results on an aggregate basis and manages our operations as a single operating segment.

Recently Issued Accounting Standards

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

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

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

2. Supplemental Financial Data

Inventories

Our inventory consisted of the following (in thousands):

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

Property, Plant and Equipment

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

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

Accrued Liabilities

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

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

3. Revenues

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

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

Revenue Sources

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

Commercial Revenue: SPINRAZA royalties and Licensing and other royalty revenue

We earn commercial revenue primarily in the form of royalty payments on net sales of SPINRAZA. We earn royalty revenue on net sales of QALSODY which is included in Licensing and other royalty revenue.

Commercial Revenue: TEGSEDI and WAYLIVRA revenue, net

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

Research and development revenue under collaboration agreements

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

Upfront payments: When we enter into a collaboration agreement and receive an upfront payment, we typically record the entire upfront payment as deferred revenue if our only performance obligation is for R&D services we will provide in the future. We amortize the upfront payment into revenue as we perform the R&D services.

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

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

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

License fees: We recognize as revenue the total amount we determine to be the relative stand-alone selling price of a license when we deliver the license to our partner who has full use of the license and we do not have any additional performance obligations related to the license after delivery.

Sublicense fees: We recognize sublicense fee revenue in the period in which a party, who has already licensed our technology, further licenses the technology to another party because we do not have any performance obligations related to the sublicense.

WAINUA (Eplontersen) Collaboration with AstraZeneca

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

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

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

We also concluded that the co-development activities, the co-commercialization activities and the co-medical affairs activities are within the scope of ASC 808 because we and AstraZeneca are active participants exposed to the risks and benefits of the activities under the collaboration and therefore do not have a vendor-customer relationship. AstraZeneca is currently responsible for 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading the Phase 3 development program, we made an accounting policy election to recognize as non-customer revenue the cost-share funding from AstraZeneca, net of our share of AstraZeneca's development expenses, in the same period we incur the related development expenses. As AstraZeneca is responsible for the majority of the commercial and medical affairs costs in the U.S. and all costs associated with bringing WAINUA to market outside the U.S., we made an accounting policy election to recognize cost-share funding we receive from AstraZeneca related to commercial and medical affairs activities as reductions of our SG&A expense and R&D expense, respectively.

4. Collaborative Arrangements and Licensing Agreements

Strategic Partnership

Biogen

We have several strategic collaborations with Biogen focused on using antisense technology to advance the treatment of neurological disorders. We developed and licensed to Biogen SPINRAZA, our approved medicine to treat people with spinal muscular atrophy, or SMA. Under our 2013 strategic neurology collaboration, Biogen developed QALSODY (tofersen), our medicine that received accelerated approval in the U.S. to treat patients with superoxide dismutase 1 amyotrophic lateral sclerosis, or SOD1-ALS. In addition, we and Biogen are currently developing numerous other investigational medicines to treat neurodegenerative diseases, including medicines in development to treat people with amyotrophic lateral sclerosis, or ALS, SMA, Angelman Syndrome, or AS, Alzheimer's disease, or AD, and Parkinson's disease, or PD. In addition to these medicines, our collaborations with Biogen include a substantial research pipeline that addresses a broad range of neurological diseases. From inception through December 31, 2023, we have received nearly $3.8 billion from our Biogen collaborations, including payments to purchase our stock.

Spinal Muscular Atrophy Collaborations

SPINRAZA

In 2012, we entered into a collaboration agreement with Biogen to develop and commercialize SPINRAZA. From inception through December 31, 2023, we earned more than $2.1 billion in total revenue under our SPINRAZA collaboration, including more than $1.6 billion in revenue from SPINRAZA royalties and more than $425 million in R&D revenue. We are receiving tiered royalties ranging from 11 percent to 15 percent on net sales of SPINRAZA. We have exclusively in-licensed patents related to SPINRAZA from Cold Spring Harbor Laboratory and the University of Massachusetts. We pay Cold Spring Harbor Laboratory and the University of Massachusetts a low single digit royalty on net sales of SPINRAZA. Biogen is responsible for all global development, regulatory and commercialization activities and costs for SPINRAZA. We completed our performance obligations under our collaboration in 2016.

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

New Antisense Medicines for the Treatment of SMA

In 2017, we entered into a collaboration agreement with Biogen to identify new antisense medicines for the treatment of SMA. Biogen has the option to license therapies arising out of this collaboration following the completion of preclinical studies. Upon licensing, Biogen will be responsible for global development, regulatory and commercialization activities and costs for such therapies.

At the commencement of this collaboration, we received a $25 million upfront payment from Biogen. In 2021, Biogen exercised its option to license ION306, a drug we discovered under this collaboration, for which we earned a $60 million license fee payment. We recognized this payment as revenue in full because Biogen had full use of the license without any continuing involvement from us. Biogen is solely responsible for the costs and expenses related to the development, manufacturing and potential future commercialization of ION306 following the option exercise. We do not have any remaining performance obligations under this collaboration. We will receive development and regulatory milestone payments from Biogen if new medicines, including ION306, advance towards marketing approval.

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

Neurology Collaborations

2018 Strategic Neurology

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

At the commencement of this collaboration, we received $1 billion from Biogen, comprised of $625 million to purchase our stock at an approximately 25 percent cash premium and $375 million in an upfront payment.

For each medicine under this collaboration, we are eligible to receive up to $270 million, which is comprised of a $15 million license fee, up to $105 million in development milestone payments and up to $150 million in regulatory milestone payments. In addition, we are eligible to receive tiered royalties up to the 20 percent range on net sales from any product that Biogen successfully commercializes under this collaboration. We are currently advancing multiple programs under this collaboration. From inception through December 31, 2023, we have received nearly $1.1 billion in payments under this collaboration, including payments to purchase our stock. We will achieve the next payment of up to $15 million if Biogen licenses a medicine under this collaboration.

We considered that the collaboration agreement and SPA were negotiated concurrently and in contemplation of one another. Based on these facts and circumstances, we concluded that we should evaluate the provisions of the agreements on a combined basis. We identified one performance obligation, which was to perform R&D services for Biogen. We determined our transaction price to be $552 million, comprised of $375 million from the upfront payment and $177 million for the premium paid by Biogen for its purchase of our common stock. We determined the fair value of the premium we received by using the stated premium in the SPA and applying a lack of marketability discount. We included a lack of marketability discount in our valuation of the premium because Biogen received restricted shares of our common stock. We allocated the transaction price to our single performance obligation.

From inception through December 31, 2023, we have included $623 million in upfront and milestone payments in the transaction price for our R&D services performance obligation under this collaboration, including a $7.5 million milestone payment we achieved in the fourth quarter of 2023. This milestone payment did not create a new performance obligation because it is part of our original R&D services performance obligation. Therefore, we included this amount in our transaction price for our R&D services performance obligation in the period we achieved the milestone payment. We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligation at the end of the contractual term in June 2028.

2013 Strategic Neurology

In 2013, we and Biogen entered into a strategic relationship focused on applying antisense technology to advance the treatment of neurodegenerative diseases. As part of the collaboration, Biogen gained exclusive rights to the use of our antisense technology to develop therapies for neurological diseases and has the option to license medicines resulting from this collaboration. In most cases, we are responsible for drug discovery and early development of antisense medicines and Biogen has the option to license antisense medicines after Phase 2 proof-of-concept. In 2016, we expanded our collaboration to include additional research activities we will perform. If Biogen exercises its option to license a medicine, it will assume global development, regulatory and commercialization responsibilities and costs for that medicine.

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

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

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

For each of the other antisense molecules that are chosen for drug discovery and development under this collaboration, we are eligible to receive up to approximately $260 million, which is comprised of a $70 million license fee, up to $60 million in development milestone payments and up to $130 million in regulatory milestone payments. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales from any product that Biogen successfully commercializes under this collaboration. From inception through December 31, 2023, we have received more than $325 million in payments under our 2013 strategic neurology collaboration. We will achieve the next payment of $70 million if Biogen licenses a medicine under this collaboration.

At the commencement of our 2013 strategic neurology collaboration, we identified one performance obligation, which was to perform R&D services for Biogen. At inception, we determined the transaction price to be the $100 million upfront payment we received and allocated it to our single performance obligation. As we achieve milestone payments for our R&D services, we include these amounts in our transaction price for our R&D services performance obligation. We recognized revenue for our R&D services performance obligation based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. During 2020, we completed our remaining R&D services and recognized the remaining revenue related to this performance obligation. From inception through the completion of our R&D services performance obligation in 2020, we included $145 million in total payments in the transaction price for our R&D services performance obligation.

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective period we generated the payment because we did not have any performance obligations for the respective payment. For example, in 2023, we earned a $16 million milestone payment from Biogen when the FDA approved Biogen's New Drug Application, or NDA, for QALSODY, which we recognized in full because we did not have any remaining performance obligations related to this milestone payment.

2012 Neurology

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

Under the terms of the agreement, we received an upfront payment of $30 million. For each program under this collaboration, we are eligible to receive up to $210 million, which is comprised of a license fee of up to $70 million, up to $10 million in development milestone payments and up to $130 million in regulatory milestone payments, plus a mark-up on the cost estimate of the Phase 1 and 2 studies. In addition, we are eligible to receive tiered royalties up to the mid-teens on net sales of any medicines resulting from each of the two programs. From inception through December 31, 2023, we have received more than $230 million in payments under this collaboration, including $39 million in milestone payments we received from Biogen for advancing ION582 during 2023 and a $10 million milestone payment we received from Biogen when Biogen advanced IONIS-MAPT$_{Rx}$ during 2022. We will achieve the next payment of $70 million if Biogen licenses ION582 under this collaboration.

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

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

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

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

Joint Development and Commercialization Arrangement

AstraZeneca

WAINUA (Eplontersen) Collaboration

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

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

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

We determined that we had a vendor-customer relationship within the scope of ASC 606 for the license we granted to AstraZeneca and as a result we had one performance obligation. For our sole performance obligation, we determined the transaction price was the $200 million upfront payment we received in 2021. In 2023, we earned a $20 million license fee payment when we licensed rights to Latin America for WAINUA to AstraZeneca. We recognized these payments in full because we did not have any remaining performance obligations after we delivered the licenses to AstraZeneca.

We also concluded that the co-development activities, the co-commercialization activities and the co-medical affairs activities are within the scope of ASC 808 because we and AstraZeneca are active participants exposed to the risks and benefits of the activities under the collaboration. AstraZeneca is currently responsible for 55 percent of the costs associated with the ongoing global Phase 3 development program. Because we are leading the Phase 3 development program, we recognize as revenue the 55 percent of cost-share funding AstraZeneca is responsible for in the same period we incur the related development expenses. As AstraZeneca is responsible for the majority of the commercial and medical affairs costs in the U.S. and all costs associated with bringing WAINUA to market outside the U.S., we recognize cost-share funding we receive from AstraZeneca related to these activities as a reduction of our commercial and medical affairs expenses. In 2023, we earned a $50 million milestone payment when the FDA approved WAINUA for ATTRv-PN in the U.S. We recognized this milestone payment in full as joint development revenue because we did not have any remaining performance obligations related to the milestone payment.

Research and Development Partners

AstraZeneca

In addition to our collaboration for WAINUA, we have a collaboration with AstraZeneca focused on discovering and developing treatments for cardiovascular, renal and metabolic diseases, which we formed in 2015. Under our collaboration, AstraZeneca has licensed multiple medicines from us. AstraZeneca is responsible for global development, regulatory and commercialization activities and costs for each of the medicines it has licensed from us.

Over the term of the collaboration, we are eligible to receive up to $3.4 billion, which is comprised of a $65 million upfront payment, up to $290 million in license fees, up to $865 million in development milestone payments and up to $2.2 billion in regulatory milestone payments. In addition, we are eligible to receive tiered royalties up to the low teens on net sales from any product that AstraZeneca successfully commercializes under this collaboration agreement. From inception through December 31, 2023, we have received more than $300 million in payments under this collaboration. We will achieve the next payment of $10 million if AstraZeneca advances a medicine under this collaboration.

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

Under this collaboration, we have also generated additional payments that we concluded were not part of our R&D services performance obligation. We recognized each of these payments in full in the respective period we generated the payment because the payments were distinct and we did not have any performance obligations for the respective payment. For example, in 2023, we earned a $36 million payment when AstraZeneca licensed ION826 from us. We recognized this payment in full in 2023 because we did not have any remaining performance obligations after we delivered the license to AstraZeneca.

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

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

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

GSK

In 2010, we entered into a collaboration with GSK using our antisense drug discovery platform to discover and develop new medicines against targets for serious and rare diseases, including infectious diseases. Upon initiating the collaboration, we received an upfront payment of $35 million. Under our collaboration, GSK is developing bepirovirsen for the treatment of chronic hepatitis B virus infection, or HBV, infection. In 2019, following positive Phase 2 results, GSK licensed our HBV program. GSK is responsible for all global development, regulatory and commercialization activities and costs for the HBV program.

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

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

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

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

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

Novartis

Pelacarsen Collaboration

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Roche

Huntington's Disease

In 2013, we entered into an agreement with Hoffmann-La Roche Inc and F. Hoffmann-La Roche Ltd, collectively Roche, to develop treatments for HD based on our antisense technology. Under the agreement, we discovered and developed tominersen, an investigational medicine targeting HTT protein. We developed tominersen through completion of our Phase 1/2 clinical study in people with early-stage HD. In 2017, upon completion of the Phase 1/2 study, Roche exercised its option to license tominersen. As a result, Roche is responsible for all global development, regulatory and commercialization activities and costs for tominersen.

Over the term of the collaboration, we are eligible to receive up to $395 million, which is comprised of a $30 million upfront payment, a $45 million license fee, up to $70 million in development milestone payments, up to $170 million in regulatory milestone payments and up to $80 million in sales milestone payments as tominersen advances. In addition, we are eligible to receive up to $136.5 million in milestone payments for each additional medicine successfully developed. We are also eligible to receive tiered royalties up to the mid-teens on net sales of any product resulting from this collaboration. From inception through December 31, 2023, we have received more than $150 million in payments under this collaboration. We will achieve the next payment of $17.5 million if Roche advances a medicine under this collaboration.

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

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

In January 2023, Roche initiated the Phase 2, GENERATION HD2, study of tominersen in patients with prodromal or early manifest HD. Roche is focusing on early-stage and younger patients based on the post-hoc analyses from the GENERATION HD1 study that suggested tominersen may benefit these patient groups. We do not have any remaining performance obligations related to tominersen under this collaboration with Roche; however, we can still earn additional payments and royalties as Roche advances tominersen.

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

In 2018, we entered into a collaboration agreement with Roche to develop IONIS-FB-L_{Rx} for the treatment of complement-mediated diseases. We are currently conducting multiple studies in two disease indications for IONIS-FB-L_{Rx}, one for the treatment of patients with immunoglobulin A, or IgA, nephropathy, or IgAN, and one for the treatment of patients with GA, the advanced stage of dry AMD. In April 2023, Roche initiated a Phase 3 study of IONIS-FB-L_{Rx} in patients with IgAN.

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

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

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

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

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

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

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

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

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

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

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

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

Commercialization Partnerships

Otsuka

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

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

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

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

We are recognizing revenue for our R&D services performance obligation as we perform services based on our effort to satisfy our performance obligation relative to our total effort expected to satisfy our performance obligation. We currently estimate we will satisfy our performance obligations in March 2026.

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

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

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

PTC Therapeutics

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

Swedish Orphan Biovitrum AB (Sobi)

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

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

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

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

Technology Enhancement Collaborations

Bicycle Therapeutics

In 2020, we entered into a collaboration agreement with Bicycle and obtained an option to license its peptide technology to potentially increase the delivery capabilities of our LICA medicines. In 2021, we paid $42 million when we exercised our option to license Bicycle's technology, which included an equity investment in Bicycle. As part of our stock purchase, we entered into a lockup agreement with Bicycle that restricted our ability to trade our Bicycle shares for one year. In 2021, we recorded a $7.2 million equity investment for the shares we received in Bicycle. We recognized the remaining $34.8 million as R&D expense in 2021.

Metagenomi

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

Other Agreements

Alnylam Pharmaceuticals, Inc.

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

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

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

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

5. Investments

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

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

As illustrated above, at December 31, 2023, 92 percent of our available-for-sale securities had a maturity of less than two years.

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

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

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

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

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

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

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

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

(3) Our privately held equity securities are included in deposits and other assets. We recognize our privately held equity securities at cost minus impairments, plus or minus changes resulting from observable price changes in orderly transactions for the identical or similar investment of the same issuer, which are Level 3 inputs. In the year ended December 31, 2023, we recorded a $2.6 million net unrealized gain in our consolidated statements of operations related to changes in the fair value of our investments in privately held companies.

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

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

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

6. Fair Value Measurements

The following tables present the major security types we held at December 31, 2023 and 2022 that we regularly measure and carry at fair value. The following tables segregate each security type by the level within the fair value hierarchy of the valuation techniques we utilized to determine the respective securities' fair value (in thousands):

	At December 31, 2023	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)
Cash equivalents (1)	$ 185,424	$ 185,424	$ —
Corporate debt securities (2)	801,228	—	801,228
Debt securities issued by U.S. government agencies (3)	334,828	—	334,828
Debt securities issued by the U.S. Treasury (3)	807,679	807,679	—
Debt securities issued by states of the U.S. and political subdivisions of the states (3)	21,155	—	21,155
Publicly traded equity securities included in other current assets (5)	6,301	6,301	—
Total	$ 2,156,615	$ 999,404	$ 1,157,211

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

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

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

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

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

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

Convertible Notes

Our 1.75% Notes, 0% Notes and 0.125% Notes had a fair value of $661.1 million, $667.8 million and $42.4 million at December 31, 2023, respectively. We determine the fair value of our notes based on quoted market prices for these notes, which are Level 2 measurements because the notes do not trade regularly.

7. Long-Term Obligations and Commitments

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

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

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

Convertible Debt and Call Spread

1.75% Convertible Senior Notes

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

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

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

0% Convertible Senior Notes and Call Spread

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

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

	0% Notes
Outstanding principal balance	$632.5
Unamortized debt issuance costs	$7.2
Maturity date	April 2026
Interest rate	0%
Effective interest rate	0.5%
Conversion price per share	$57.84
Effective conversion price per share with call spread	$76.39
Total shares of common stock subject to conversion	10.9

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

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our consolidated balance sheets. Refer to Note 1, *Organization and Significant Accounting Policies*, for our Call Spread accounting policy. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

0.125% Convertible Senior Notes and Call Spread

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

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

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

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

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

We recorded the amount we paid for the note hedges and the amount we received for the warrants in additional paid-in capital in our consolidated balance sheets. Refer to Note 1, *Organization and Significant Accounting Policies*, for our Call Spread accounting policy. We reassess our ability to continue to classify the note hedges and warrants in shareholders' equity at each reporting period.

Other Terms of Convertible Senior Notes

The 1.75%, 0% and 0.125% Notes are convertible under certain conditions, at the option of the note holders. We can settle conversions of the notes, at our election, in cash, shares of our common stock or a combination of both. We may not redeem the notes prior to maturity, and we do not have to provide a sinking fund for them. Holders of the notes may require us to purchase some or all of their notes upon the occurrence of certain fundamental changes, as set forth in the indentures governing the notes, at a purchase price equal to 100 percent of the principal amount of the notes to be purchased, plus any accrued and unpaid interest.

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

Financing Arrangements

Operating Facilities

In 2017, we purchased the building that houses our primary R&D facility for $79.4 million and our manufacturing facility for $14.0 million. We financed the purchase of these two facilities with mortgage debt of $60.4 million in total. Our primary R&D facility mortgage had an interest rate of 3.88 percent. Our manufacturing facility mortgage has an interest rate of 4.20 percent. During the first five years of both mortgages, we were only required to make interest payments. We began making principal payments in 2022. Our manufacturing facility mortgage matures in August 2027. We repaid our primary R&D facility mortgage in 2022 in conjunction with a sale and leaseback transaction.

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

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

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

Debt Maturity Schedules

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

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

Operating Leases

Carlsbad Leases

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

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

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

Oceanside Lease

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

Boston Leases

We entered into an operating lease agreement for office space located in Boston, Massachusetts which commenced in August 2018. We are leasing this space under a non-cancelable operating lease with an initial term ending after 123 months and an option to extend the lease for an additional five-year term. Under the lease agreement, we received a three-month free rent period.

In 2022, we entered into a sublease agreement for our office space located in Boston, Massachusetts. The sublease commencement date was in January 2022 when the office space was ready for our tenant's occupancy. We are subleasing this space under a non-cancelable operating sublease with a sublease term ending 83 months following the sublease commencement date with no option to extend the sublease. Under the sublease agreement we provided a seven-month free rent period, which commenced in January 2022. We will receive lease payments over the sublease term totaling $9.6 million.

We entered into an operating lease agreement for another office space located in Boston, Massachusetts which commenced in 2021. We are leasing this space under a non-cancelable operating lease with an initial term ending 91 months following the lease commencement date and an option to extend the lease for an additional five-year term. Under the lease agreement, we received a seven-month free rent period, which commenced in November 2021. Our lease payments over the initial term total $6.8 million.

When we determined our lease term for our operating lease right-of-use assets and lease liabilities for these leases, we did not include the extension options for these leases in the original lease term because it was not reasonably certain we would exercise those extension options.

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

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

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

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

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

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

Royalty Revenue Monetization

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

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

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

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

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

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

8. Stockholders' Equity

Preferred Stock

We are authorized to issue up to 15 million shares of "blank check" Preferred Stock. As of December 31, 2023, there were no shares of Preferred Stock outstanding. We have designated Series C Junior Participating Preferred Stock but have no issued or outstanding shares as of December 31, 2023.

Common Stock

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

During the years ended December 31, 2023, 2022 and 2021, we issued 2.3 million, 1.2 million and 1.1 million shares of common stock, respectively, for stock option exercises, vesting of restricted stock units, and ESPP purchases. We received net proceeds from these transactions of $49.4 million, $6.4 million and $11.6 million in 2023, 2022 and 2021, respectively.

Stock Plans

1989 Stock Option Plan

In 1989, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that, as amended, provides for the issuance of non-qualified and incentive stock options for the purchase of up to 20.0 million shares of common stock to our employees, directors, and consultants. The plan expires in January 2024. The 1989 Stock Option Plan, or 1989 Plan, does not allow us to grant stock bonuses or restricted stock awards and prohibits us from repricing any options outstanding under the plan unless our stockholders approve the repricing. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. At December 31, 2023, no options were outstanding and 68,000 shares were available for future grant under the 1989 Plan.

2011 Equity Incentive Plan

In 2011, our Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that provides for the issuance of stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, and performance cash awards to our employees, directors, and consultants. In June 2015, May 2017 and June 2019, after receiving approval from our stockholders, we amended our 2011 Equity Incentive Plan, or 2011 Plan, to increase the total number of shares reserved for issuance. We increased the shares available under our 2011 Equity Incentive Plan from 5.5 million to 11.0 million in June 2015, from 11.0 million to 16.0 million in May 2017 and from 16.0 million to 23.0 million in June 2019. In June 2021, after receiving approval from our stockholders, we amended our 2011 Plan. The amendment increased the total number of shares of common stock authorized for issuance under the 2011 Plan from 23.0 million to 29.7 million and added a fungible share counting ratio whereby the share reserve will be reduced by 1.7 shares for each share of common stock issued pursuant to a full value award (i.e., RSU or PRSU) and increased by 1.7 shares for each share of common stock returning from a full value award. In June 2023, after receiving approval from our stockholders, we amended our 2011 Plan to increase the total number of shares of common stock authorized for issuance under the 2011 Plan from 29.7 million to 35.2 million.

The plan expires in June 2031. The 2011 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only stock options, RSU and PRSU awards to our employees, directors and consultants. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. Options granted after December 31, 2021 have a term of ten years. We have granted restricted stock unit awards to our employees under the 2011 Plan which vest annually over a four-year period. At December 31, 2023, a total of 12.8 million options were outstanding, of which 8.7 million were exercisable, 3.3 million restricted stock unit awards were outstanding, and 8.0 million shares were available for future grant under the 2011 Plan.

Under the 2011 Plan, we may issue a stock award with additional acceleration of vesting and exercisability upon or after a change in control. In the absence of such provisions, no such acceleration will occur. In addition, we implemented a change of control and severance benefit plan that provides for change of control and severance benefits to our executive officers, including our chief executive officer and chief financial officer, and vice presidents. If one of our executive officers or vice presidents is terminated or resigns for good reason during the period that begins three months before and ends twelve months following a change in control of the company, the impacted employee's stock options and RSUs vesting will accelerate for options and RSUs outstanding as of the termination date.

2020 Equity Incentive Plan

In connection with the Akcea Merger in 2020, we assumed the unallocated portion of the available share reserve under the Akcea 2015 Equity Incentive Plan. In 2020, we amended and restated the Akcea 2015 equity plan, including renaming the plan as the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan, or 2020 Plan. The 2020 Plan provided for the issuance of up to 2.6 million shares of our Common Stock to our employees, directors and consultants who were employees of Akcea prior to the Akcea Merger. In the second quarter of 2021, our Compensation Committee approved an amendment to the 2020 Plan. The amendment decreased the total number of shares of common stock authorized for issuance under the 2020 Plan from approximately 2.6 million to 1.6 million. We assumed the 2020 Plan in connection with Ionis' reacquisition of all of the outstanding shares of Akcea Therapeutics, Inc. as part of the Akcea Merger.

The plan expires in December 2025. The 2020 Plan does not allow us to reduce the exercise price of any outstanding stock options or stock appreciation rights or cancel any outstanding stock options or stock appreciation rights that have an exercise price or strike price greater than the current fair market value of the common stock in exchange for cash or other stock awards unless our stockholders approve such action. Currently we anticipate awarding only stock options and RSU awards to our eligible employees, directors and consultants. Options vest over a four-year period, with 25 percent exercisable at the end of one year from the date of the grant and the balance vesting ratably, on a monthly basis, thereafter and have a term of seven years. Options granted after December 31, 2021 have a term of ten years. We have granted restricted stock unit awards to our employees under the 2020 Plan which vest annually over a four-year period. At December 31, 2023, a total of 0.4 million options were outstanding, of which 0.1 million were exercisable, 0.2 million restricted stock unit awards were outstanding, and 1.0 million shares were available for future grant under the 2020 Plan.

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

Corporate Transactions and Change in Control under 2011 and 2020 Plans

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

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

2002 Non-Employee Directors' Stock Option Plan

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

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

Options under this plan expire 10 years from the date of grant. At December 31, 2023, a total of 0.9 million options were outstanding, of which 0.9 million were exercisable, 40,000 restricted stock unit awards were outstanding, and 0.5 million shares were available for future grant under the 2002 Plan.

Employee Stock Purchase Plan

In 2009, our Board of Directors adopted, and the stockholders subsequently approved, the amendment and restatement of the ESPP and we reserved an additional 150,000 shares of common stock for issuance thereunder. In each of the subsequent years until 2019, we reserved an additional 150,000 shares of common stock for the ESPP resulting in a total of 3.2 million shares authorized under the plan as of December 31, 2023. The ESPP permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10 percent of each employee's compensation) at the lower of 85 percent of fair market value at the beginning of the purchase period or the end of each purchase period. Under the amended and restated ESPP, employees must hold the stock they purchase for a minimum of six months from the date of purchase. During 2023, employees purchased and we issued to employees 0.1 million shares under the ESPP at a weighted average price of $30.53 per share. At December 31, 2023, there were 0.4 million shares available for purchase under the ESPP.

Stock Option Activity

The following table summarizes the stock option activity under our stock plans for the year ended December 31, 2023 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Exercise Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2022	14,970	$ 50.57		
Granted	2,407	$ 38.80		
Exercised	(1,444)	$ 45.06		
Cancelled/forfeited/expired	(1,842)	$ 55.90		
Outstanding at December 31, 2023	14,091	$ 48.43	4.74	$ 78,542
Exercisable at December 31, 2023	9,703	$ 52.24	3.20	$ 28,349

The weighted-average estimated fair values of options granted were $19.72, $18.66 and $24.35 for the years ended December 31, 2023, 2022 and 2021, respectively. The total intrinsic value of options exercised during the years ended December 31, 2023, 2022 and 2021 were $6.0 million, $1.4 million and $2.5 million, respectively, which we determined as of the date of exercise. The amount of cash received from the exercise of stock options was $65.1 million, $3.6 million and $8.5 million for the years ended December 31, 2023, 2022 and 2021, respectively. For the year ended December 31, 2023, the weighted-average fair value of options exercised was $49.23. As of December 31, 2023, total unrecognized compensation cost related to non-vested stock options was $36.6 million. We expect to recognize this cost over a weighted average period of 1.1 years. We will adjust the total unrecognized compensation cost for future changes in estimated forfeitures.

Restricted Stock Unit Activity

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

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

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

Performance Restricted Stock Unit Activity

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

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

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

Stock-based Compensation Expense and Valuation Information

The following table summarizes stock-based compensation expense for the years ended December 31, 2023, 2022 and 2021 (in thousands):

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

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

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

Employee Stock Options:

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

Board of Director Stock Options:

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

ESPP:

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

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

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

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

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

Forfeitures. We reduce stock-based compensation expense for estimated forfeitures. We estimate forfeitures at the time of grant and revise, if necessary, in subsequent periods if actual forfeitures differ from those estimates. We estimate forfeitures based on historical experience.

9. Income Taxes

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

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

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

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

Our expense (benefit) for income taxes differs from the amount computed by applying the U.S. federal statutory rate to loss before income taxes. The sources and tax effects of the differences are as follows (in thousands):

	Year Ended December 31,					
	2023		2022		2021	
Pre-tax loss	$ (333,965)		$ (257,985)		$ (29,148)	
Statutory rate	(70,133)	21.0%	(54,177)	21.0%	(6,121)	21.0%
State income tax net of federal benefit	(22,597)	6.8%	(13,622)	5.3%	4,278	(14.7)%
Foreign	(22)	0.0%	(49)	0.0%	143	(0.5)%
Net change in valuation allowance	175,388	(52.5)%	104,951	(40.7)%	2,885	(9.9)%
Loss on debt transactions	—	—	—	—	262	(0.9)%
Tax credits	(67,131)	20.1%	(39,729)	15.4%	(23,198)	79.6%
Deferred tax true-up	4	0.0%	(20)	0.0%	(24)	0.1%
Tax rate change	1,023	(0.3)%	(3,091)	1.2%	12,838	(44.0)%
Non-deductible compensation	3,814	(1.1)%	3,023	(1.2)%	5,085	(17.4)%
Other non-deductible items	327	(0.1)%	57	0.0%	84	(0.3)%
Foreign-derived intangible income benefit	(7,493)	2.2%	—	—	—	—
Stock-based compensation	19,546	(5.9)%	14,030	(5.4)%	4,720	(16.2)%
Other	(405)	0.1%	364	(0.1)%	(1,503)	5.1%
Effective rate	$ 32,321	(9.7)%	$ 11,737	(4.5)%	$ (551)	1.9%

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes.

Significant components of our deferred tax assets and liabilities as of December 31, 2023 and 2022 are as follows (in thousands):

	Year Ended December 31,	
	2023	2022
Deferred Tax Assets:		
Net operating loss carryovers	$ 77,964	$ 87,802
Tax credits	239,962	277,436
Deferred revenue	71,683	85,700
Stock-based compensation	77,468	86,983
Intangible and capital assets	104,380	104,649
Convertible debt	16,849	34,384
Capitalized research and development expenses	238,738	119,635
Long-term lease liabilities	43,718	45,612
Sale of future royalties	144,608	—
Other	10,343	15,813
Total deferred tax assets	$ 1,025,713	$ 858,014
Deferred Tax Liabilities:		
Fixed assets	(4,166)	(4,475)
Right-of-use assets	(42,007)	(44,504)
Other	(1,910)	(313)
Net deferred tax asset	$ 977,630	$ 808,722
Valuation allowance	(977,630)	(808,722)
Total net deferred tax assets and liabilities	$ —	$ —

We evaluate our deferred tax assets regularly to determine whether adjustments to the valuation allowance are appropriate due to changes in facts or circumstances, such as changes in expected future pre-tax earnings, tax law, interactions with taxing authorities and developments in case law. In making this evaluation, we rely on our recent history of pre-tax earnings. Our material assumptions are our forecasts of future pre-tax earnings and the nature and timing of future deductions and income represented by the deferred tax assets and liabilities, all of which involve the exercise of significant judgment. Although we believe our estimates are reasonable, we are required to use significant judgment in determining the appropriate amount of valuation allowance recorded against our deferred tax assets.

Our valuation allowance increased by $169 million from December 31, 2022 to December 31, 2023. The increase was primarily related to increases in our deferred tax assets for capitalized research and development expenses and sale of future royalties.

At December 31, 2023, we had federal and state, primarily California, tax net operating loss carryforwards of $242.8 million and $398.8 million, respectively. Our federal tax loss carryforwards are available indefinitely. Our California tax loss carryforwards will begin to expire in 2032. At December 31, 2023, we also had federal and California research and development tax credit carryforwards of $169.7 million and $124.4 million, respectively. Our federal research and development tax credit carryforwards will begin to expire in 2038. Our California research and development tax credit carryforwards are available indefinitely. Our 2023 current tax expense includes a benefit of approximately $3.2 million related to utilization of state tax loss carryforwards, primarily California.

Utilization of the net operating loss and tax credit carryforwards may be subject to an annual limitation due to the ownership change limitations provided by the Internal Revenue Code of 1986, as amended, and similar state provisions. The annual limitation may result in the expiration of net operating losses and credits before utilization.

We analyze filing positions in all U.S. federal, state and foreign jurisdictions where we file income tax returns, and all open tax years in these jurisdictions to determine if we have any uncertain tax positions on any of our income tax returns. We recognize the impact of an uncertain tax position on an income tax return at the largest amount that the relevant taxing authority is more-likely-than not to sustain upon audit. We do not recognize uncertain income tax positions if they have less than 50 percent likelihood of the applicable tax authority sustaining our position.

The following table summarizes our gross unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2023	2022	2021
Beginning balance of unrecognized tax benefits	$ 56,567	$ 55,085	$ 54,163
Decrease for lapse of statute of limitations	(14,993)	—	—
Decrease for prior period tax positions	(737)	(267)	(695)
Increase for prior period tax positions	429	259	263
Increase for current period tax positions	2,032	1,490	1,354
Ending balance of unrecognized tax benefits	$ 43,298	$ 56,567	$ 55,085

Included in the balance of unrecognized tax benefits at December 31, 2023, 2022 and 2021 was $0.3 million, $6.2 million and $6.2 million respectively, that if we recognized, could impact our effective tax rate, subject to our remaining valuation allowance.

We estimate that it is reasonably possible that the balance of our gross unrecognized tax benefits may decrease by approximately $7.6 million within the next 12 months due to the lapse of statute of limitations on underlying tax positions primarily related to amortization of certain capitalized state research and development expenditures.

We recognize interest and/or penalties related to income tax matters in income tax expense. During the years ended December 31, 2023, 2022 and 2021, we recognized $0.1 million, $0.8 million and $0.5 million, respectively, of accrued interest and penalties related to gross unrecognized tax benefits.

We are subject to taxation in the U.S. and various state and foreign jurisdictions. U.S. tax years 2020 through 2022 remain open to examination and tax years 2019 through 2022 remain open to examination by major state taxing jurisdictions, primarily California, although net operating loss and credit carryforwards generated prior to these periods may still be adjusted upon examination by the Internal Revenue Service or state tax authorities if they have been used in an open period or are used in a future period.

10. Employment Benefits

We have employee 401(k) salary deferral plans covering all employees. Employees could make contributions by withholding a percentage of their salary up to the IRS annual limits of $22,500 and $30,000 in 2023 for employees under 50 years old and employees 50 years old or over, respectively. We made approximately $7.1 million, $5.6 million and $5.5 million in matching contributions for the years ended December 31, 2023, 2022 and 2021, respectively.

11. Legal Proceedings

From time to time, we are involved in legal proceedings arising in the ordinary course of our business. Periodically, we evaluate the status of each legal matter and assess our potential financial exposure. If we consider the potential loss from any legal proceeding to be probable and we can reasonably estimate the amount, we accrue a liability for the estimated loss. The outcome of any proceeding is not determinable in advance. Therefore, we are required to use significant judgment to determine the probability of a loss and whether the amount of the loss is reasonably estimable. Our assessment of a potential liability and the amount of accruals we recorded are based only on the information available to us at the time. As additional information becomes available, we reassess the potential liability related to the legal proceeding and may revise our estimates.

There are no pending material legal proceedings to which we are a party or of which our property is the subject.

12. Fourth Quarter Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized fourth quarter data for 2023 and 2022 are as follows (in thousands, except per share data).

Three Months Ended December 31,	2023	2022
Revenue (1)	$ 324,505	$ 151,890
Operating expenses (2)	$ 330,627	$ 359,909
Loss from operations	$ (6,122)	$ (208,019)
Net loss (3)	$ (9,263)	$ (52,430)
Basic net loss per share (4) (5)	$ (0.06)	$ (0.37)
Diluted net loss per share (4) (6)	$ (0.06)	$ (0.37)

(1) Revenue was higher in the three months ended December 31, 2023 compared to the same period in 2022 primarily due to the $50 million milestone payment we earned from AstraZeneca when the FDA approved WAINUA for ATTRv-PN in the U.S., $36 million payment we earned when AstraZeneca licensed ION826 and revenue we recognized in the fourth quarter of 2023 from the upfront payments we received from our new collaborations with Otsuka, Roche and Novartis.

(2) Operating expenses were lower in the three months ended December 31, 2023 compared to the same period in 2022 primarily due to the $80 million upfront payment we made for our collaboration with Metagenomi in the fourth quarter of 2022.

(3) Our net loss for the three months ended December 31, 2022 includes the $150.1 million gain we recognized from the sale and leaseback transaction for our headquarters in Carlsbad, California.

(4) We compute net loss per share independently for each quarter during the year.

(5) As discussed in Note 1, *Organization and Significant Accounting Policies,* we compute basic net loss per share by dividing the total net loss by our weighted-average number of common shares outstanding during the period.

(6) We incurred a net loss for the fourth quarter of 2023 and 2022. As a result, we did not include dilutive common equivalent shares in the computation of diluted net loss per share because the effect would have been anti-dilutive.