

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and are not soliciting an offer to buy these securities in any state or other jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED SEPTEMBER 9, 2024

PRELIMINARY PROSPECTUS SUPPLEMENT
(To Prospectus dated November 24, 2023)

\$500,000,000



Common Stock

Ionis Pharmaceuticals, Inc. is offering \$500,000,000 of shares of its common stock.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "IONS." Assuming a public offering price of \$46.89 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on September 6, 2024, we would be offering 10,663,254 shares.

PRICE \$ A SHARE

	Underwriting Discounts and Commissions ⁽¹⁾	Proceeds to Us
Per Share	\$	\$
Total	\$	\$

(1) See the section titled "Underwriters" for additional information regarding compensation payable to the underwriters.

We have granted the underwriters an option for a period of 30 days to purchase up to an additional \$75,000,000 of shares of common stock from us.

Neither the Securities and Exchange Commission nor any other state securities commission has approved or disapproved of these securities or passed on the adequacy or accuracy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

Investing in our common stock involves risks that are described in the "[Risk Factors](#)" section beginning on page S-8 of this prospectus supplement and under similar headings in the documents that are incorporated by reference into this prospectus supplement and the accompanying prospectus.

The underwriters expect to deliver the shares of common stock to purchasers on September , 2024.

Joint Book-Running Managers

Morgan Stanley

Goldman Sachs & Co. LLC

September , 2024

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Prospectus

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus relate to an offering of our common stock. Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus supplement and the accompanying prospectus, together with the information incorporated by reference as described under the headings “Where You Can Find More Information” and “Incorporation of Certain Information by Reference” in this prospectus supplement. These documents contain important information that you should consider when making your investment decision.

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to, updates and changes information contained in the accompanying prospectus and the documents incorporated by reference herein and therein. The second part is the accompanying prospectus, which gives more general information, some of which may not be applicable to this offering. To the extent the information contained in this prospectus supplement differs from or conflicts with the information contained in the accompanying prospectus or any document incorporated by reference herein or therein, the information in this prospectus supplement will control. If any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference into this prospectus supplement or the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

We have not, and the underwriters have not, authorized anyone else to provide you with information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, along with the information contained in any free writing prospectus we have authorized for use in connection with this offering. We take, and the underwriters take, no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. You should read this prospectus supplement and the accompanying prospectus, as well as the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety, before making an investment decision.

Neither we nor the underwriters have done anything that would permit this offering or possession or distribution of this prospectus supplement and the accompanying prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons who come into possession of this prospectus supplement, the accompanying prospectus and any free writing prospectus related to this offering in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement, the accompanying prospectus and any such free writing prospectus applicable to that jurisdiction.

Unless the context otherwise requires, all references in this prospectus supplement to “we,” “us,” “our,” “our company” and “Ionis” refer to Ionis Pharmaceuticals, Inc. and its consolidated subsidiaries, unless otherwise specified.

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein may include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement or the accompanying prospectus are the property of their respective owners. Ionis, the Ionis logo and our other registered or common law trade names, trademarks or service marks appearing in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein are the property of Ionis Pharmaceuticals, Inc. or exclusively licensed for Ionis’ use. Solely for convenience, trademarks and tradenames referred to in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein may appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner will not assert its rights, to these trademarks and tradenames.

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary does not contain all the information you should consider before investing in our common stock. You should read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus (including the documents incorporated by reference herein and therein), including the factors described under the heading "Risk Factors" in this prospectus supplement, the accompanying prospectus and the financial and other information incorporated by reference in this prospectus supplement and the accompanying prospectus, as well as the information included in any free writing prospectus that we have authorized for use in connection with this offering, before making an investment decision.

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.

We are using our multiple sources of revenue and our capital structure 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 an antisense medicine 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 June 30, 2024, we have earned more than \$2.2 billion in revenues from our SPINRAZA collaboration, including more than \$1.7 billion in royalties on sales of SPINRAZA.

QALSODY is an antisense medicine that received accelerated approval from the United States, or U.S., Food and Drug Administration, or FDA, in April 2023 and marketing authorization under exceptional circumstances from the European Medicines Agency, or EMA, in May 2024 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.

WAINUA is a once monthly, self-administered subcutaneous LIgand-Conjugated Antisense, or LICA, medicine that received approval from the FDA in December 2023 and Health Canada in June 2024 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. We anticipate a regulatory decision from the EMA for WAINUA for the treatment of ATTRv-PN in the second half of 2024. We also anticipate additional regulatory approvals outside the U.S. in 2024. 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 is our medicine to treat patients with transthyretin amyloidosis, or ATTR, that is approved in the U.S. and Canada 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 January 2024, we launched WAINUA for the treatment of adults with ATTRv-PN in the U.S. 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 the 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 expected in 2026. 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 June 2024, the FDA accepted our NDA for patients with FCS for Priority Review with a Prescription Drug User Fee Act, or PDUFA, date of December 19, 2024. We expect to launch olezarsen in the U.S. for the treatment of FCS by the end of 2024. Additionally, we are currently preparing to submit an application in 2024 for regulatory approval for FCS in Europe. In April 2024, we opened our Expanded Access Program for patients with FCS in the U.S. Additionally, in April 2024, we presented positive Phase 3 Balance study data in patients with FCS and the Phase 2b Bridge study in patients with HTG and sHTG at the American College of Cardiology, or ACC, annual meeting with a simultaneous publication in the *New England Journal of Medicine*, or *NEJM*. *In the Balance study, Olezarsen demonstrated substantial reductions in apoC-III, TGs, marked acute pancreatitis reductions, substantial reduction in hospitalizations and favorable safety and tolerability. 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), which achieved full enrollment in 2024 and for which we expect data in 2025. The FDA granted Breakthrough Therapy designation, Orphan Drug designation and Fast Track designation to olezarsen for the treatment of FCS.

Donidalorsen is our medicine in development for hereditary angioedema, or HAE. In May 2024, we presented positive data from the Phase 3 OASIS-HAE study in patients treated every four weeks and every eight weeks at the European Academy of Allergy and Clinical Immunology 2024 Congress. In addition, we presented positive data from OASISplus, our trial that includes an open-label, or OLE, cohort for patients rolling over from the Phase 3 study and a separate cohort for patients who have transitioned to donidalorsen from other prophylactic HAE medications that we refer to as the “switch study,” with simultaneous publications in *NEJM*. In December 2023 and June 2024, we licensed commercialization rights for donidalorsen to Otsuka Pharmaceutical Co., Ltd., or Otsuka, in Europe and the Asia-Pacific region, respectively. Throughout 2022 and 2023, we reported positive data from the Phase 2 study and Phase 2 OLE study, including two-year OLE data. We submitted the NDA to the FDA in August 2024. Otsuka is preparing to submit a Marketing Authorization Application, or MAA, to the EMA, which we anticipate to occur in 2024. We anticipate the launch of donidalorsen in the U.S. for the treatment of HAE in 2025. 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 July 2024, we completed enrollment in the Phase 3 portion of the ongoing study for patients with AxD. We anticipate data from this study in 2025. 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 for which we anticipate data in 2026. In August 2023 and September 2023, the FDA and EMA, respectively, granted Orphan Drug designation to ulefnersen.

QALSODY is our marketed medicine to treat patients with SOD1-ALS. In April 2023, the FDA granted Biogen accelerated approval and in May 2024, the EMA granted Biogen marketing authorization under exceptional circumstances of QALSODY for patients with SOD1-ALS. Additionally, Biogen is evaluating QALSODY as a potential treatment for presymptomatic SOD1-ALS patients in the ongoing ATLAS study for which we anticipate data in 2028. 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)-driven cardiovascular disease. Novartis is developing pelacarsen, including conducting the ongoing Lp(a) HORIZON Phase 3 cardiovascular outcome study in patients with elevated Lp(a)-driven cardiovascular disease, which achieved full enrollment in July 2022 with more than 8,000 patients and for which we anticipate data in 2025. In April 2020, the FDA granted Fast Track designation to pelacarsen. Our partner, Novartis, has stated they anticipate submitting for regulatory approval in 2025, assuming the data are supportive.

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, which achieved full enrollment in June 2024 and for which we anticipate data in 2026. 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 for the treatment of patients with HBV.

IONIS-FB-L_{Rx} is our medicine in development for immunoglobulin A, or IgA, nephropathy, or IgAN. 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.

Potential Upcoming U.S. Approvals for Certain Drugs in Ionis' Pipeline¹

<u>Drug (target)/Indication</u>	<u>2024-2025</u>	<u>2026-2027</u>	<u>2028+</u>
Olezarsen (APOCIII)/FCS	✓		
Donidalorsen (PKK)/HAE	✓		
WAINUA (TTR)/ATTR <i>Cardiomyopathy</i>		✓	
Olezarsen (APOCIII)/sHTG		✓	
Pelacarsen /Lp(a) CVD		✓	
Bepirovirsen (HBV)/HBV <i>Infection</i>		✓	
Zilganersen (GFAP)/Alexander <i>Disease</i>		✓	
Ulefnersen (FUS)/FUS-ALS		✓	
IONIS-FB-L_{Rx} (Factor B)/IgA <i>Nephropathy</i>		✓	
Sapablursen (TMPRSS6)/ <i>Polycythemia Vera</i>			✓
Next Wave Neurology Medicines			✓
ION582 (UBE3A)/ <i>Angelman syndrome</i>			✓

(1) Any potential U.S. regulatory approval and related estimated timing are based on current assumptions and subject to risks and change.

Recent Mid-Stage Pipeline Developments

- ION582 - Angelman's Syndrome
 - Reported positive data from the Phase 2 portion of the Phase 1/2a HALOS study of ION582 (UBE3A) in patients with Angelman syndrome at the Angelman Syndrome Foundation meeting in July 2024, including:
 - Consistent improvements in key areas of clinical function, including communication, cognition and motor function,
 - Evidence of consistent improvements across age groups and genotypes, and
 - A favorable safety and tolerability profile.
 - Expect to meet with the FDA for an end of Phase 2 meeting in the second half of 2024.
 - Anticipate initiating Phase 3 development of ION582 in the first half of 2025.
- Presented positive Phase 2 data of ION224 (DGAT2) in patients with metabolic dysfunction-associated steatohepatitis.
- Initiated the Phase 1b Orbit study of ION356 (PLP1) in patients with Pelizaeus-Merzbacher disease.
- Expect ION440 (MECP2) and an undisclosed genetic dementia target to enter clinical development in 2024.
- Discontinued development of IONIS-FB-L_{Rx} for geographic atrophy (GA) and ION541 for amyotrophic lateral sclerosis (ALS) following completion of Phase 2 studies showing favorable safety profiles and good target engagement, but insufficient efficacy to advance into Phase 3 development.

Certain Other Medicines for High Patient Need in Development

Sapablursen is our medicine in development for polycythemia vera, or PV. In December 2021, we initiated a Phase 2 study evaluating sapablursen in patients with phlebotomy dependent PV. In January 2024, the FDA granted Fast Track designation to sapablursen for PV.

Corporate Information

We incorporated in California on January 10, 1989. In conjunction with our initial public offering, we reorganized as a Delaware corporation in April 1991. In December 2015, we changed our name from Isis Pharmaceuticals, Inc. to Ionis Pharmaceuticals, Inc. Our principal executive offices are located at 2855 Gazelle Court, Carlsbad, CA 92010, and our telephone number is (760) 931-9200. We maintain a website at www.ionis.com. Information contained on, or that can be accessed through, our website is not incorporated by reference into this prospectus supplement and the accompanying prospectus.

THE OFFERING

Common stock offered by us	\$500.0 million of shares.
Option to purchase additional shares	We have granted the underwriters an option to purchase up to an additional \$75.0 million of shares of our common stock. This option is exercisable, in whole or in part, for a period of 30 days following the date of this prospectus supplement.
Common stock to be outstanding immediately after this offering	Assuming a public offering price of \$46.89 per share, the last reported sale price of our common stock on the Nasdaq Global Select Market on September 6, 2024, 156,688,500 shares (or 158,287,988 shares if the underwriters exercise their option to purchase additional shares in full).
Use of proceeds	<p>We estimate that we will receive net proceeds from this offering of approximately \$ million (or approximately \$ million if the underwriters exercise their option to purchase additional shares in full), after deducting underwriting discounts and commissions and estimated offering expenses payable by us.</p> <p>We intend to use the net proceeds we receive from this offering, together with our existing cash, cash equivalents and short-term investments, to fund our independent commercial launches, late-stage clinical programs, earlier pipeline programs, and research and development activities, as well as for working capital and general corporate purposes. See the section titled “Use of Proceeds” for additional information.</p>
Risk factors	See the section titled “Risk Factors” and other information included or incorporated by reference in this prospectus supplement and the accompanying prospectus for additional information.
Nasdaq Global Select Market symbol	“IONS.”

The number of shares of our common stock that will be outstanding after this offering is based on 146,025,246 shares of common stock outstanding as of June 30, 2024, and excludes:

- 15,060,842 shares of common stock issuable upon the exercise of options to purchase shares of common stock outstanding as of June 30, 2024, with a weighted-average exercise price of \$48.51 per share;
- 3,706,672 shares of common stock issuable upon vesting and settlement of restricted stock units outstanding as of June 30, 2024;
- 307,102 shares of common stock issuable upon vesting and settlement of performance restricted stock units outstanding as of June 30, 2024;
- 28,227,980 shares of our common stock issuable upon conversion of our convertible notes outstanding as of June 30, 2024;
- 17,526,080 shares of common stock issuable upon the exercise of our warrants outstanding as of June 30, 2024;

- 27,918,988 shares of common stock reserved for future issuance under our 2002 Non-Employee Directors' Stock Option Plan, or 2002 plan, 2011 Equity Incentive Plan, or 2011 Plan, and our 2020 Equity Incentive Plan, or 2020 Plan, as of June 30, 2024; and
- 311,969 shares of common stock reserved for future issuance under our 2000 Employee Stock Purchase Plan, or 2000 ESPP, as of June 30, 2024.

Subsequent to June 30, 2024 and through August 30, 2024:

- we granted stock options to purchase 243,659 shares of common stock with a weighted-average exercise price of \$47.62 per share; and
- we granted restricted stock units to acquire 225,531 shares of common stock.

Unless otherwise indicated, the information in this prospectus supplement assumes:

- no exercise or settlement, as applicable, of the outstanding stock options, restricted stock units or performance restricted stock units summarized above;
- no conversion or exercise, as applicable, of the outstanding convertible notes or warrants summarized above; and
- no exercise of the underwriters' option to purchase up to \$75.0 million of additional shares of our common stock.

RISK FACTORS

Investing in our common stock 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. Before deciding whether to invest in our common stock, you should consider carefully the risk factors discussed below and those contained in the section titled “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2023 and our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2024 and June 30, 2024, each as filed with the Securities and Exchange Commission, or SEC, and incorporated herein by reference in its entirety.

Risks Related to this Offering

Management will have broad discretion as to the use of the net proceeds from this offering, and may not use the proceeds effectively.

Our management will have broad discretion in the application of the net proceeds we receive from this offering, including for any of the purposes described in the section titled “Use of Proceeds,” and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. Our management could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Our failure to apply these funds effectively could have a material adverse effect on our business, financial condition and results of operations, delay the development of our product candidates and cause the price of our common stock to decline.

You will experience immediate and substantial dilution in the book value per share of the common stock you purchase in this offering.

Since the price per share of our common stock being offered in this offering is substantially higher than the net tangible book value per share of our common stock outstanding prior to this offering, you will suffer substantial dilution with respect to the net tangible book value of the common stock you purchase in this offering. Based on the public offering price of \$ per share and our net tangible book value as of June 30, 2024, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of \$ per share (or \$ per share if the underwriters exercise their option to purchase additional shares in full) with respect to the as adjusted net tangible book value of the common stock. The exercise of outstanding stock options, the settlement of restricted stock units or performance restricted stock units, or the issuance of common stock upon conversion or exercise, as applicable, of our convertible notes or warrants may result in further dilution of your investment. See the section titled “Dilution” for a more detailed discussion of the dilution you will incur if you purchase common stock in this offering.

You may experience future dilution as a result of future financings.

In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per share in this offering. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by investors in this offering.

We do not intend to pay dividends on our common stock, so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividend on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

If securities or industry analysts do not continue to publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our stock, our stock price and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that industry or securities analysts publish about us or our business. If any of the analysts who cover us issue an adverse or misleading opinion regarding us, our business model, our intellectual property or our stock performance, or if our clinical trials and operating results fail to meet the expectations of analysts, our stock price will likely decline. In addition, if one or more of these analysts cease coverage of us or fail to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

Future sales of our common stock in the public market, or the perception that such sales could occur, could cause our stock price to fall.

The sale of a substantial number of shares of our common stock or other equity-related securities in the public markets, or the perception that such sales could occur, could depress the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities. We may sell large quantities of our common stock at any time pursuant to this prospectus supplement or in one or more separate offerings. We cannot predict the effect that future sales of common stock or other equity-related securities would have on the market price of our common stock.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated herein and therein by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or Securities Act, and Section 21E of the Securities Exchange Act of 1934, or Exchange Act. All statements other than statements of historical facts contained in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein are forward-looking statements. These forward-looking statements include, but are not limited to, statements regarding our business and the therapeutic and commercial potential of our marketed medicines, including SPINRAZA (nusinersen), QALSODY (tofersen), WAINUA (eplontersen), TEGSEDI (inotersen) and WAYLIVRA (volanesorsen), as well as our additional medicines in development and technologies, the achievement of potential regulatory approvals for our medicines in development and the anticipated timing of any such approvals. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including, but not limited to, those related to our commercial products and the medicines in our pipeline, 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 our Annual Report on Form 10-K for the year ended December 31, 2023, our Quarterly Report on Form 10-Q for the periods ended March 31, 2024 and June 30, 2024, our Current Reports on Form 8-K and our other filings with the SEC. 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. In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus supplement, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain, and you are cautioned not to unduly rely upon these statements. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. We claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 for all forward-looking statements.

USE OF PROCEEDS

We estimate that we will receive net proceeds from this offering of approximately \$ million (or approximately \$ million if the underwriters exercise their option to purchase an additional shares in full), after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds we receive from this offering, together with our existing cash, cash equivalents and short-term investments, to fund our independent commercial launches, late-stage clinical programs, earlier pipeline programs, and research and development activities, as well as for working capital and general corporate purposes.

This expected use of the net proceeds from this offering represents our intentions based on our current plans and business conditions, which could change in the future as our plans and business conditions evolve. Further, due to the uncertainties inherent in discovering, developing and commercializing medicines, it is difficult to estimate with certainty the exact amounts of the net proceeds from this offering that may be used for the above purposes. We cannot specify with certainty all of the particular uses for the remaining net proceeds to us from this offering. We may also use a portion of the net proceeds for acquisitions or strategic investments in complementary businesses, products, services or technologies or in connection with partnering and manufacturing arrangements. We will have broad discretion over how to use the net proceeds from this offering, and our investors will be relying on the judgment of our management regarding the application of the net proceeds of this offering. The amounts and timing of our expenditures will depend upon numerous factors, including the 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, and our manufacturing requirements and capacity to fulfill such requirements.

We intend to invest the net proceeds from this offering that are not used as described above in short- and intermediate-term, interest-bearing obligations, investment-grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

DIVIDEND POLICY

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all available funds and future earnings, if any, to fund the development and expansion of our business, and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination regarding the declaration and payment of dividends will be at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant. In addition, we may enter into agreements in the future that could contain restrictions on payments of cash dividends.

CAPITALIZATION

The following table sets forth our cash, cash equivalents and short-term investments, our short-term indebtedness and our capitalization as of June 30, 2024 as follows:

- on an actual basis; and
- on an as adjusted basis, giving effect to the issuance and sale of _____ shares of common stock in this offering at the public offering price of \$ _____ per share.

You should read this information in conjunction with our consolidated financial statements and related notes and the section titled “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2023, our Quarterly Report on Form 10-Q for the quarter ended March 31, 2024 and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, each as incorporated by reference in this prospectus supplement and the accompanying prospectus.

	As of June 30, 2024	
	Actual	As Adjusted
Cash and cash equivalents	\$ 293,993	\$ _____
Short-term investments	1,784,693	_____
Cash, cash equivalents and short-term investments	<u>\$ 2,078,686</u>	<u>\$ _____</u>
Short-term indebtedness:		
0.125% convertible senior notes due 2024 ⁽¹⁾	\$ 44,504	\$ _____
Long-term indebtedness:		
0% convertible senior notes due 2026 ⁽¹⁾	\$ 632,500	\$ _____
1.75% convertible senior notes due 2028 ⁽¹⁾	575,000	_____
Long-term mortgage debt	8,626	_____
Liability related to sale of future royalties, net	533,754	_____
Long-term lease liabilities	166,438	_____
Long-term obligations	41,773	_____
Stockholders’ equity:		
Common stock, \$0.001 par value; 300,000,000 shares authorized, 146,025,246 and _____ shares issued and outstanding, actual and as adjusted ⁽²⁾	\$ 146	\$ _____
Additional paid-in capital	2,303,369	_____
Accumulated other comprehensive loss	(34,838)	_____
Accumulated deficit	(2,004,979)	_____
Total stockholders’ equity	<u>263,698</u>	<u>_____</u>
Total capitalization	<u>\$ 2,221,789</u>	<u>\$ _____</u>

(1) Reflects the aggregate principal amount of the notes without reflecting issuance costs that we are required to recognize.

(2) The outstanding share information in the table above is based on 146,025,246 shares of common stock outstanding as of June 30, 2024, and excludes:

- 15,060,842 shares of common stock issuable upon the exercise of options to purchase shares of common stock outstanding as of June 30, 2024, with a weighted-average exercise price of \$48.51 per share;
- 3,706,672 shares of common stock issuable upon vesting and settlement of restricted stock units outstanding as of June 30, 2024;
- 307,102 shares of common stock issuable upon vesting and settlement of performance restricted stock units outstanding as of June 30, 2024;

-
- 28,227,980 shares of our common stock issuable upon conversion of our convertible notes outstanding as of June 30, 2024;
 - 17,526,080 shares of common stock issuable upon the exercise of our warrants outstanding as of June 30, 2024;
 - 27,918,988 shares of common stock reserved for future issuance under our 2002 Plan, our 2011 Plan and our 2020 Plan, as of June 30, 2024; and
 - 311,969 shares of common stock reserved for future issuance under our 2000 ESPP as of June 30, 2024.

Subsequent to June 30, 2024 and through August 30, 2024:

- we granted stock options to purchase 243,659 shares of common stock with a weighted-average exercise price of \$47.62 per share; and
- we granted restricted stock units to acquire 225,531 shares of common stock.

DILUTION

If you invest in our common stock in this offering, your ownership interest will be immediately diluted to the extent of the difference between the public offering price per share and the as adjusted net tangible book value per share of our common stock after this offering.

Our net tangible book value as of June 30, 2024 was \$19.3 million, or \$0.13 per share of our common stock. Our net tangible book value represents the amount of our total tangible assets less our total liabilities. Net tangible book value per share represents net tangible book value, which is our tangible assets, less our total liabilities, divided by the number of shares of our common stock outstanding as of June 30, 2024.

After giving effect to the sale of _____ shares of common stock that we are offering at the public offering price of \$ _____ per share of common stock and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2024, would have been \$ _____ million, or \$ _____ per share of our common stock. This amount represents an immediate increase in as adjusted net tangible book value of \$ _____ per share to our existing stockholders and an immediate dilution in net tangible book value of \$ _____ per share to new investors purchasing shares of common stock in this offering.

Dilution per share to new investors is determined by subtracting as adjusted net tangible book value per share after this offering from the price per share paid by new investors. The following table illustrates this dilution (without giving effect to any exercise by the underwriters of their option to purchase additional shares of our common stock):

Public offering price per share	\$
Historical net tangible book value per share as of June 30, 2024	\$0.13
Increase in net tangible book value per share attributable to this offering	<u> </u>
As adjusted net tangible book value per share as of June 30, 2024, after giving effect to this offering	<u> </u>
Dilution per share to new investors in this offering	<u>\$</u>

If the underwriters exercise their option to purchase up to an additional _____ shares of our common stock in full, the as adjusted net tangible book value after the offering would be \$ _____ per share, the increase in net tangible book value per share to existing stockholders would be \$ _____ per share and the dilution per share to new investors would be \$ _____ per share.

The above discussion and table are based on 146,025,246 shares of our common stock outstanding as of June 30, 2024, and exclude:

- 15,060,842 shares of common stock issuable upon the exercise of options to purchase shares of common stock outstanding as of June 30, 2024, with a weighted-average exercise price of \$48.51 per share;
- 3,706,672 shares of common stock issuable upon vesting and settlement of restricted stock units outstanding as of June 30, 2024;
- 307,102 shares of common stock issuable upon vesting and settlement of performance restricted stock units outstanding as of June 30, 2024;
- 28,227,980 shares of our common stock issuable upon conversion of our convertible notes outstanding as of June 30, 2024;
- 17,526,080 shares of common stock issuable upon the exercise of our warrants outstanding as of June 30, 2024;

- 27,918,988 shares of common stock reserved for future issuance under our 2002 Plan, our 2011 Plan and our 2020 Plan, as of June 30, 2024; and
- 311,969 shares of common stock reserved for future issuance under our 2000 ESPP as of June 30, 2024.

Subsequent to June 30, 2024 and through August 30, 2024:

- we granted stock options to purchase 243,659 shares of common stock with a weighted-average exercise price of \$47.62 per share; and
- we granted restricted stock units to acquire 225,531 shares of common stock.

To the extent any outstanding options are exercised, any outstanding restricted stock units or performance restricted stock units are settled, any outstanding convertible notes are converted, any outstanding warrants are exercised, or new options, restricted stock units, performance restricted stock units or other equity awards are issued under our equity incentive plans, or we issue additional equity or convertible debt securities in the future, there will be further dilution to new investors.

**MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO
NON-U.S. HOLDERS OF OUR COMMON STOCK**

The following summary describes the material U.S. federal income tax consequences of the ownership and disposition of our common stock acquired in this offering by Non-U.S. Holders (as defined below). This discussion is not a complete analysis of all potential U.S. federal income tax consequences relevant to a Non-U.S. Holder's particular circumstances, and does not deal with non-U.S., state and local tax consequences that may be relevant to Non-U.S. Holders, nor does it address any U.S. federal tax consequences (such as gift and estate taxes) other than income taxes. Special rules different from those described below may apply to certain Non-U.S. Holders that are subject to special treatment under the U.S. Internal Revenue Code of 1986, as amended, or Code, such as financial institutions, insurance companies, tax-exempt organizations, brokers, dealers and certain electing traders in securities who mark their securities positions to market for U.S. tax purposes, certain former U.S. citizens or long-term residents, "controlled foreign corporations," "passive foreign investment companies," corporations that accumulate earnings to avoid U.S. federal income tax, corporations organized outside of the United States, any state thereof or the District of Columbia that are nonetheless treated as U.S. income taxpayers for U.S. federal tax purposes, persons that hold our common stock as part of a "straddle," "conversion transaction," "synthetic security" or integrated investment or other risk reduction strategy, persons subject to the alternative minimum tax, the federal Medicare contribution tax on net investment income or the special tax accounting rules under Section 451(b) of the Code, "qualified foreign pension funds" as defined in Section 897(l)(2) of the Code and entities all of the interests of which are held by qualified foreign pension funds, partnerships and other pass-through entities or arrangements, and investors in such pass-through entities or arrangements. Such Non-U.S. Holders are urged to consult their tax advisors to determine the U.S. federal, state, local and other tax consequences that may be relevant to them. In addition, this discussion assumes that the Non-U.S. Holder holds our common stock as a "capital asset" within the meaning of Section 1221 of the Code (generally, property held for investment). Furthermore, the discussion below is based upon the provisions of the Code, Treasury regulations promulgated thereunder, rulings and judicial decisions, in each case as of the date hereof, and such authorities may be repealed, revoked or modified, perhaps retroactively, so as to result in U.S. federal income tax consequences different from those discussed below. We have not requested a ruling from the U.S. Internal Revenue Service, or IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions.

Persons considering the purchase of our common stock pursuant to this offering should consult their tax advisors concerning the U.S. federal income, estate and other tax consequences of acquiring, owning and disposing of our common stock in light of their particular situations as well as any consequences arising under the laws of any other taxing jurisdiction, including any state, local or non-U.S. tax consequences.

For the purposes of this discussion, a "Non-U.S. Holder" is, for U.S. federal income tax purposes, a beneficial owner of common stock that is neither a U.S. Person, nor a partnership (or other entity treated as a partnership for U.S. federal income tax purposes regardless of its place of organization or formation). A "U.S. Person" means any person that is, for U.S. federal income tax purposes, any of the following:

- an individual who is a citizen or resident of the United States;
- a corporation or other entity treated as a corporation for U.S. federal income tax purposes created or organized in or under the laws of the United States, any state thereof or the District of Columbia;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust if it (1) is subject to the primary supervision of a court within the United States and one or more "United States persons" (within the meaning of Code Section 7701(a)(30)) have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable Treasury regulations to be treated as a United States person.

In the case of a beneficial owner of our common stock that is classified as a partnership for U.S. federal income tax purposes, the tax treatment of a person treated as a partner in such partnership for U.S. federal income tax purposes generally will depend on the status of the partner, the activities of the partner and the partnership and certain determinations made at the partner level. A person treated as a partner in a partnership or who holds our common stock through another pass-through entity should consult his, her or its tax advisor regarding the tax consequences of the ownership and disposition of our common stock through a partnership or other pass-through entity, as applicable.

Distributions

Distributions, if any, made on our common stock to a Non-U.S. Holder to the extent made out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles) generally will constitute dividends for U.S. tax purposes and will be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty, subject to the discussions below regarding effectively connected income, backup withholding and foreign accounts. To obtain a reduced rate of withholding under an income tax treaty, a Non-U.S. Holder generally will be required to provide its withholding agent with a properly executed IRS Form W-8BEN (in the case of individuals) or IRS Form W-8BEN-E (in the case of entities), or other appropriate form, certifying the Non-U.S. Holder's entitlement to benefits under that treaty and, in certain circumstances, providing such Non-U.S. Holder's U.S. taxpayer identification number and/or foreign tax identifying number. This certification must be provided prior to the payment of dividends and may need to be updated in certain circumstances. In the case of a Non-U.S. Holder that is an entity, Treasury regulations and the relevant income tax treaty provide rules to determine whether, for purposes of determining the applicability of an income tax treaty, dividends will be treated as paid to the entity or to those holding an interest in that entity. If a Non-U.S. Holder holds our common stock through a financial institution or other agent acting on its behalf, it will be required to provide appropriate documentation to such agent, which will then be required to provide certification to the applicable withholding agent, either directly or through other intermediaries. If the Non-U.S. Holder is eligible for a reduced rate of U.S. federal withholding tax under an income tax treaty and does not timely file the required certification, it may be able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS. Non-U.S. Holders should consult their tax advisors regarding their entitlement to benefits under any applicable income tax treaty.

We and other withholding agents are not required to withhold tax on dividends paid to a Non-U.S. Holder that are effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment or fixed base that it maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished prior to the payment of such dividends. In general, such effectively connected dividends will be subject to U.S. federal income tax, on a net income basis at the regular rates applicable to U.S. Persons. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional "branch profits tax," which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable income tax treaty) on the corporate Non-U.S. Holder's effectively connected earnings and profits, subject to certain adjustments. Non-U.S. Holders should consult their tax advisors regarding any applicable income tax treaties that may provide for different rules.

To the extent distributions on our common stock, if any, exceed our current and accumulated earnings and profits, they will first reduce the Non-U.S. Holder's adjusted basis in our common stock, but not below zero, and then will be treated as capital gain to the extent of any excess, and taxed in the same manner as gain realized from a sale or other disposition of common stock as described in the next section.

Gain on Disposition of Our Common Stock

Subject to the discussions below regarding backup withholding and foreign accounts, a Non-U.S. Holder generally will not be subject to U.S. federal income tax with respect to gain realized on a sale or other disposition

of our common stock unless (a) the gain is effectively connected with a trade or business of the Non-U.S. Holder in the United States (and, if required by an applicable income tax treaty, is attributable to a permanent establishment or fixed base that such Non-U.S. Holder maintains in the United States), (b) the Non-U.S. Holder is a nonresident alien individual and is present in the United States for 183 or more days in the taxable year of the disposition and certain other conditions are met or (c) we are or have been a “United States real property holding corporation,” or USRPHC, within the meaning of Code Section 897(c)(2) at any time within the shorter of the five-year period preceding such disposition and such Non-U.S. Holder’s holding period. In general, we would be a USRPHC if the aggregate fair market value of our “United States real property interests” (within the meaning of Code Section 897(c)(1)), or USRPIs, equaled or exceeded fifty percent (50%) of the combined fair market value of our USRPIs, our non-U.S. real property interests and our other business assets. We believe that we have not been and are not, and do not anticipate becoming, a USRPHC. Even if we are or were to become a USRPHC, gain realized by a Non-U.S. Holder on a disposition of our common stock will not be subject to U.S. federal income tax so long as (1) the Non-U.S. Holder owned, directly, indirectly and constructively, no more than five percent of our common stock at all times within the shorter of (i) the five-year period preceding the disposition and (ii) the Non-U.S. Holder’s holding period and (2) our common stock is “regularly traded,” as defined by applicable Treasury regulations, on an established securities market. There can be no assurance that we are not or will not become a USRPHC or that our common stock will qualify as regularly traded on an established securities market.

Gain described in (a) above will generally be subject to U.S. federal income tax at rates applicable to U.S. Persons, and corporate Non-U.S. Holders may, in addition, be subject to a branch profits tax at a 30% rate, or such lower rate as may be specified by an applicable income tax treaty, on such effectively connected gain, as adjusted for certain items. A Non-U.S. Holder described in (b) above will be subject to U.S. federal income tax at a flat 30% rate, or such lower rate as may be specified by an applicable income tax treaty, on gain realized upon the sale or other taxable disposition, which gain may be offset by certain U.S.-source capital losses of the Non-U.S. Holder (even though the Non-U.S. Holder is not considered a resident of the United States), provided that the Non-U.S. Holder has timely filed U.S. federal income tax returns with respect to such losses.

Information Reporting Requirements and Backup Withholding

Generally, we or an applicable withholding agent will be required to report information to the IRS with respect to any distributions we pay on our common stock (even if the payments are exempt from withholding), including the amount of any such distributions, the name and address of the recipient, and the amount, if any, of tax withheld. A similar report is sent to the Non-U.S. Holder to whom any such distributions are paid. Pursuant to tax treaties or certain other agreements, the IRS may make its reports available to tax authorities in the recipient’s country of residence.

Distributions to a Non-U.S. Holder that are classified as dividends paid by us may also be subject to U.S. backup withholding currently at a rate of 24%. U.S. backup withholding generally will not apply to a Non-U.S. Holder who provides a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E, or IRS Form W-8ECI, or otherwise establishes an exemption. Notwithstanding the foregoing, backup withholding may apply if the applicable payor has actual knowledge, or reason to know, that the Non-U.S. Holder is a U.S. Person who is not an exempt recipient.

U.S. information reporting and backup withholding requirements generally will apply to the proceeds of a sale or other taxable disposition of our common stock effected by or through a U.S. office of any broker, U.S. or foreign, except that information reporting and such requirements may be avoided if the Non-U.S. Holder provides a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E or IRS Form W-8ECI, or otherwise meets documentary evidence requirements for establishing non-U.S. Person status or otherwise establishes an exemption. Generally, U.S. information reporting and backup withholding requirements will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a non-U.S. broker. Information reporting and backup withholding requirements

may, however, apply to a payment of disposition proceeds if the payor has actual knowledge, or reason to know, that the Non-U.S. Holder is, in fact, a U.S. Person. For information reporting purposes, certain brokers with substantial U.S. ownership or operations will generally be treated in a manner similar to U.S. payors.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or credit against the U.S. federal income tax liability of a Non-U.S. Holder subject to backup withholding, provided that the required information is timely furnished to the IRS.

Foreign Accounts

Sections 1471 through 1474 of the Code and the related Treasury regulations, together with other U.S. Treasury and IRS guidance issued thereunder and intergovernmental agreements, legislation, rules and other official guidance adopted pursuant to such intergovernmental agreements (commonly referred to as FATCA) impose a U.S. federal withholding tax of 30% on certain payments to a “foreign financial institution” (as defined in the Code) which does not provide the withholding agent with sufficient documentation evidencing either (x) an exemption from FATCA or (y) its compliance (or deemed compliance) with FATCA (which may alternatively be in the form of compliance with an intergovernmental agreement with the United States) to withhold on certain payments and to collect and provide to the U.S. tax authorities certain information regarding U.S. account holders of such institution (which includes certain equity holders of such institution, as well as certain account holders that are foreign entities with U.S. owners). FATCA also generally imposes a federal withholding tax of 30% on certain payments to a non-financial foreign entity (as defined in the Code) which does not provide the withholding agent with sufficient documentation evidencing either (x) an exemption from FATCA or (y) either a certification that it does not have any substantial direct or indirect U.S. owners or provides information regarding substantial direct and indirect U.S. owners of the entity. An intergovernmental agreement between the United States and an applicable foreign country may modify those requirements. The withholding tax described above will not apply if the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from the rules. Prospective investors are encouraged to consult with their tax advisors regarding the possible implications of FATCA on their investment in our common stock.

The withholding provisions described above generally apply to payments of dividends. Under proposed Treasury regulations, the preamble to which states that taxpayers may rely on them until final Treasury regulations are issued, this withholding tax does not apply to payments of gross proceeds from a sale or other disposition of common stock.

EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS TAX ADVISOR REGARDING THE TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES OF ANY CHANGES IN APPLICABLE LAW SUBSEQUENT TO THE DATE HEREOF.

UNDERWRITERS

Under the terms and subject to the conditions in an underwriting agreement dated the date of this prospectus supplement, the underwriters named below, for whom Morgan Stanley & Co. LLC and Goldman Sachs & Co. LLC are acting as representatives, have severally agreed to purchase, and we have agreed to sell to them, severally, the number of shares indicated below:

Name	Number of Shares
Morgan Stanley & Co. LLC	
Goldman Sachs & Co. LLC	
Total	

The underwriters are offering the shares of common stock subject to their acceptance of the shares from us and subject to prior sale. The underwriting agreement provides that the obligations of the several underwriters to pay for and accept delivery of the shares of common stock offered by this prospectus supplement are subject to the approval of certain legal matters by their counsel and to certain other conditions. The underwriters are obligated to take and pay for all of the shares of common stock offered by this prospectus supplement if any such shares are taken. However, the underwriters are not required to take or pay for the shares covered by the underwriters' option to purchase additional shares described below.

The underwriters initially propose to offer part of the shares of common stock directly to the public at the offering price listed on the cover page of this prospectus supplement and part to certain dealers at a price that represents a concession not in excess of \$ per share. After the initial offering of the shares of common stock, the offering price and other selling terms may from time to time be varied by the representatives.

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus supplement, to purchase up to additional shares of common stock at the public offering price listed on the cover page of this prospectus supplement, less underwriting discounts and commissions. To the extent the option is exercised, each underwriter will become obligated, subject to certain conditions, to purchase about the same percentage of the additional shares of common stock as the number listed next to the underwriter's name in the preceding table bears to the total number of shares of common stock listed next to the names of all underwriters in the preceding table.

The following table shows the per share and total public offering price, underwriting discounts and commissions, and proceeds before expenses. These amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase up to an additional shares of common stock.

	Per Share	Total	
		No Exercise	Full Exercise
Public offering price	\$	\$	\$
Underwriting discounts and commissions			
Proceeds, before expenses, to us	\$	\$	\$

The estimated offering expenses payable by us, exclusive of the underwriting discounts and commissions, are approximately \$. We have agreed to reimburse the underwriters for certain of their expenses in an amount up to \$7,500.

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol "IONS."

We have agreed that, without the prior written consent of Morgan Stanley & Co. LLC and Goldman Sachs & Co. LLC on behalf of the underwriters, we will not, and will not publicly disclose the intention to, during the period ending 45 days after the date of this prospectus supplement, or restricted period, (1) offer, issue, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise transfer or dispose of, directly or indirectly, or file with the Securities and Exchange Commission a registration statement under the Securities Act relating to any of our securities that are substantially similar to the common stock, including but not limited to any securities that are convertible into, exercisable or exchangeable for, or that represent the right to receive, common stock or any such substantially similar securities, or (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the common stock or any such other securities, whether any such transaction is to be settled by delivery of common stock or such other securities, in cash or otherwise (other than (A) the shares of common stock offered hereby, (B) pursuant to equity incentive plans existing on, or pursuant to the terms of securities convertible, exercisable or exchangeable for common stock or other substantially similar securities outstanding as of the date of this prospectus supplement and disclosed in this prospectus supplement, (C) pursuant to the terms of securities exercisable for common stock issued after the date of prospectus supplement pursuant to equity incentive plans existing on the date of this prospectus supplement and disclosed in this prospectus supplement, (D) registration statements on Form S-8 or any successor form, (E) the entry into an agreement providing for the issuance of, or the actual issuance of, shares of common stock or securities that are convertible into, exercisable or exchangeable for, or that represent the right to receive common stock, in connection with one or more license agreements, collaboration agreements or joint ventures; provided that in the case of this clause (E), the aggregate number of shares of common stock that we may issue or sell or agree to issue or agree to sell shall not exceed 5% of the total number of shares of common stock issued and outstanding as of the date of this prospectus supplement, and that we shall (1) cause each recipient of such securities to execute and deliver to the representatives, on or prior to the issuance of such securities, a lock-up agreement, and (2) enter stop transfer instructions with the transfer agent and registrar on such securities, which we agree not to waive or amend without the prior written consent of the representatives.

In addition, our directors and executive officers, or each, a lock-up party, have agreed that, without the prior written consent of Morgan Stanley & Co. LLC and Goldman Sachs & Co. LLC on behalf of the underwriters, such lock-up parties will not, and will not publicly disclose the intention to, during the restricted period, (i) offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise dispose of any shares of common stock, or any options or warrants to purchase any shares of common stock, or any securities convertible into, exchangeable for or that represent the right to receive shares of common stock, whether now owned or hereinafter acquired, owned directly by the lock-up party (including holding as a custodian) or with respect to which the lock-up party has beneficial ownership within the rules and regulations of the SEC, (ii) enter into any hedging, swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the common stock or such other securities, whether any such transaction described in clause (i) or (ii) above is to be settled by delivery of Common Stock or such other securities, in cash or otherwise, or (iii) make any demand for, or exercise any right with respect to, the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for shares of our common stock.

The restrictions described in the immediately preceding paragraph do not apply to: (A) transfers (i) as a bona fide gift or gifts, (ii) to any trust for the direct or indirect benefit of such lock-up party or his or her immediate family, provided that any such transfer shall not involve a disposition for value, (iii) upon death by will or intestacy or (iv) pursuant to a court order or a settlement agreement related to the distribution of assets in connection with the dissolution of a marriage or civil union, provided that in the case of clauses (A)(i)—(A)(iv), the transferee agrees to be bound by the lock-up restrictions and as a result of any such transfer, no public reports, including but not limited to public reports pursuant to Section 16(a) of the Exchange Act are required to be or are voluntarily filed by any such lock-up party in connection with such transfer during the restricted period (other than a filing in the case of a transfer pursuant to clauses (A)(i) and A(iv) required pursuant to Section 16(a) of the Exchange Act; provided that, with respect to a transfer pursuant to clause (A)(i), any such filing shall state that such transfer is a bona fide gift and, with respect to transfers pursuant to clause (A)(i) and (A)(iv), such

securities remain subject to the lock-up restrictions; (B) transfers pursuant to any contract, instruction or plan in effect on the date hereof complying with Rule 10b5-1 under the Exchange Act, or Rule 10b5-1, and of which the underwriters or their counsel have been made aware; (C) entry into a Rule 10b5-1 plan after the date hereof; provided that (i) such plan does not provide for the transfer of our common stock during the restricted period, (ii) to the extent a public announcement or filing under the Exchange Act, if any, is required to be made by or on behalf of such lock-up party or us regarding the establishment of such plan, such announcement or filing shall include a statement to the effect that no transfer of such lock-up party's securities may be made under such plan during the restricted period and (iii) no public announcement or filing under the Exchange Act regarding the establishment of such plan shall otherwise be required of or voluntarily made during the restricted period; (D) transfers to us in connection with the repurchase of securities issued pursuant to our equity incentive plans or pursuant to agreements pursuant to which such securities were issued; (E) transfers or sales with the prior written consent of the representatives on behalf of the underwriters; (F) transfers pursuant to a bona fide third-party tender offer, merger, consolidation or other similar transaction that is approved by our board of directors and made to all holders of our capital stock involving a change of control of us, provided that in the event that such tender offer, merger, consolidation or other similar transaction is not completed, the securities shall remain subject to the lock-up restrictions; and (G) transfers to us pursuant to a cashless or net exercise of a security issued pursuant to our equity incentive plans to cover the exercise price or taxes due upon the exercise or vesting of securities; and (G) sales effected by the administrator of our equity incentive plans to cover taxes due in connection with the vesting of restricted stock units issued pursuant to such plans. The lock-up agreements shall not restrict the receipt, exercise, vesting, forfeiture of, or removal or lapse of restrictions on any shares of our common stock or equity incentive awards pursuant to any equity incentive plan outstanding as of the date of this prospectus supplement, provided that such transaction does not involve the sale or transfers of shares of our common stock other than as provided in this paragraph.

Morgan Stanley & Co. LLC and Goldman Sachs & Co. LLC, in their sole discretion, may release the common stock and other securities subject to the lock-up agreements described above in whole or in part at any time.

In order to facilitate the offering of the common stock, the underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the common stock. Specifically, the underwriters may sell more shares than they are obligated to purchase under the underwriting agreement, creating a short position. A short sale is covered if the short position is no greater than the number of shares available for purchase by the underwriters under the option. The underwriters can close out a covered short sale by exercising the option or purchasing shares in the open market. In determining the source of shares to close out a covered short sale, the underwriters will consider, among other things, the open market price of shares compared to the price available under the option. The underwriters may also sell shares in excess of the option, creating a naked short position. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in this offering. As an additional means of facilitating this offering, the underwriters may bid for, and purchase, shares of common stock in the open market to stabilize the price of the common stock. These activities may raise or maintain the market price of the common stock above independent market levels or prevent or retard a decline in the market price of the common stock. The underwriters are not required to engage in these activities and may end any of these activities at any time.

We and the underwriters have agreed to indemnify each other against certain liabilities, including liabilities under the Securities Act.

A prospectus supplement in electronic format may be made available on websites maintained by one or more underwriters, or selling group members, if any, participating in this offering. The representatives may agree to allocate a number of shares of common stock to underwriters for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters that may make Internet distributions on the same basis as other allocations.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Certain of the underwriters and their respective affiliates have, from time to time, performed, and may in the future perform, various financial advisory and investment banking services for us, for which they received or will receive customary fees and expenses.

In addition, in the ordinary course of their various business activities, the underwriters and their respective affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers and may at any time hold long and short positions in such securities and instruments. Such investment and securities activities may involve our securities and instruments. The underwriters and their respective affiliates may also make investment recommendations or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long or short positions in such securities and instruments.

Selling Restrictions

European Economic Area

In relation to each Member State of the European Economic Area (each, a Relevant State) no shares have been offered or will be offered pursuant to the offering to the public in that Relevant State prior to the publication of a prospectus in relation to the shares which has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that offers of shares may be made to the public in that Relevant State at any time under the following exemptions under the Prospectus Regulation:

- (a) to any legal entity which is a qualified investor as defined under Article 2 of the Prospectus Regulation;
- (b) to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or
- (c) in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of shares shall require us or any representative to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation, and each person who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with each of the representatives and us that it is a “qualified investor” within the meaning of Article 2(e) of the Prospectus Regulation. In the case of any shares being offered to a financial intermediary as that term is used in the Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Relevant State to qualified investors as so defined or in circumstances in which the prior consent of the representatives have been obtained to each such proposed offer or resale.

For the purposes of this provision, the expression an “offer to the public” in relation to the shares in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase or subscribe for any shares, and the expression “Prospectus Regulation” means Regulation (EU) 2017/1129 (as amended).

United Kingdom

No shares have been offered or will be offered pursuant to the offering to the public in the United Kingdom prior to the publication of a prospectus in relation to the shares which has been approved by the Financial Conduct Authority, except that offers of shares may be made to the public in the United Kingdom at any time under the following exemptions under the UK Prospectus Regulation:

- (a) to any legal entity which is a qualified investor as defined under Article 2 of the UK Prospectus Regulation;
- (b) to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the UK Prospectus Regulation), subject to obtaining the prior consent of the representatives for any such offer; or
- (c) in any other circumstances falling within Section 86 of the Financial Services and Markets Act 2000, or FSMA,

provided that no such offer of shares shall require us or any representative to publish a prospectus pursuant to Section 85 of the FSMA or supplement a prospectus pursuant to Article 23 of the UK Prospectus Regulation.

For the purposes of this provision, the expression an “offer to the public” in relation to the shares in the United Kingdom means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase or subscribe for any shares, and the expression “UK Prospectus Regulation” means Regulation (EU) 2017/1129 as it forms part of domestic law by virtue of the European Union (Withdrawal) Act 2018.

In addition, in the United Kingdom, this prospectus supplement and the accompanying prospectus are being distributed only to, and are directed only at, and any offer subsequently made may only be directed at persons who are “qualified investors” (as defined in the Prospectus Regulation) (i) who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended, or the Order, and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as “relevant persons”) or otherwise in circumstances which have not resulted and will not result in an offer to the public of the shares in the United Kingdom within the meaning of the Financial Services and Markets Act 2000.

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons.

Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser’s province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser’s province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Singapore

This prospectus supplement and the accompanying prospectus have not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement, the accompanying prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than:

- (a) to an institutional investor (as defined in Section 4A of the Securities and Futures Act (Chapter 289) of Singapore, as modified or amended from time to time, or SFA) pursuant to Section 274 of the SFA;
- (b) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA; or
- (c) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- (d) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- (e) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities or securities-based derivatives contracts (each term as defined in Section 2(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

- (i) to an institutional investor or to a relevant person, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(c)(ii) of the SFA;
- (ii) where no consideration is or will be given for the transfer;
- (iii) where the transfer is by operation of law;
- (iv) as specified in Section 276(7) of the SFA; or
- (v) as specified in Regulation 37A of the Securities and Futures (Offers of Investments) (Securities and Securities-based Derivatives Contracts) Regulations 2018.

Switzerland

This prospectus supplement and the accompanying prospectus do not constitute an offer to the public or a solicitation to purchase or invest in any shares. No shares have been offered or will be offered to the public in Switzerland, except that offers of shares may be made to the public in Switzerland at any time under the following exemptions under the Swiss Financial Services Act, or FinSA:

- (a) to any person which is a professional client as defined under the FinSA;

- (b) to fewer than 500 persons (other than professional clients as defined under the FinSA), subject to obtaining the prior consent of the representatives for any such offer; or
- (c) in any other circumstances falling within Article 36 FinSA in connection with Article 44 of the Swiss Financial Services Ordinance,

provided that no such offer of shares shall require us or any investment bank to publish a prospectus pursuant to Article 35 FinSA.

The shares have not been and will not be listed or admitted to trading on a trading venue in Switzerland.

Neither this prospectus supplement, the accompanying prospectus nor any other offering or marketing material relating to the shares constitutes a prospectus as such term is understood pursuant to the FinSA and neither this prospectus supplement, the accompanying prospectus nor any other offering or marketing material relating to the shares may be publicly distributed or otherwise made publicly available in Switzerland.

Japan

The shares have not been and will not be registered pursuant to Article 4, Paragraph 1 of the Financial Instruments and Exchange Act. Accordingly, none of the shares nor any interest therein may be offered or sold, directly or indirectly, in Japan or to, or for the benefit of, any “resident” of Japan (which term as used herein means any person resident in Japan, including any corporation or other entity organized under the laws of Japan), or to others for re-offering or resale, directly or indirectly, in Japan or to or for the benefit of a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Act and any other applicable laws, regulations and ministerial guidelines of Japan in effect at the relevant time.

Hong Kong

The shares have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to “professional investors” as defined in the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong), or SFO, of Hong Kong and any rules made thereunder; or (b) in other circumstances which do not result in the document being a “prospectus” as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32) of Hong Kong, or CO, or which do not constitute an offer to the public within the meaning of the CO. No advertisement, invitation or document relating to the shares has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” as defined in the SFO and any rules made thereunder.

Australia

This prospectus supplement and the accompanying prospectus:

- (a) do not constitute a disclosure document or a prospectus under Chapter 6D.2 of the Corporations Act 2001 (Cth), or Corporations Act;
- (b) have not been, and will not be, lodged with the Australian Securities and Investments Commission, or ASIC, as a disclosure document for the purposes of the Corporations Act and do not purport to include the information required of a disclosure document for the purposes of the Corporations Act; and
- (c) may only be provided in Australia to select investors who are able to demonstrate that they fall within one or more of the categories of investors, available under section 708 of the Corporations Act, or Exempt Investors.

The shares may not be directly or indirectly offered for subscription or purchased or sold, and no invitations to subscribe for or buy the shares may be issued, and no draft or definitive prospectus, advertisement or other offering material relating to any shares may be distributed in Australia, except where disclosure to investors is not required under Chapter 6D of the Corporations Act or is otherwise in compliance with all applicable Australian laws and regulations. By submitting an application for the shares, you represent and warrant to us that you are an Exempt Investor.

As any offer of shares under this prospectus supplement and the accompanying prospectus will be made without disclosure in Australia under Chapter 6D.2 of the Corporations Act, the offer of those shares for resale in Australia within 12 months may, under section 707 of the Corporations Act, require disclosure to investors under Chapter 6D.2 if none of the exemptions in section 708 applies to that resale. By applying for the shares you undertake to us that you will not, for a period of 12 months from the date of sale of the shares, offer, transfer, assign or otherwise alienate those shares to investors in Australia except in circumstances where disclosure to investors is not required under Chapter 6D.2 of the Corporations Act or where a compliant disclosure document is prepared and lodged with ASIC.

Bermuda

Shares may be offered or sold in Bermuda only in compliance with the provisions of the Investment Business Act of 2003 of Bermuda, which regulates the sale of securities in Bermuda. Additionally, non-Bermudian persons (including companies) may not carry on or engage in any trade or business in Bermuda unless such persons are permitted to do so under applicable Bermuda legislation.

LEGAL MATTERS

The validity of the shares of common stock being offered by this prospectus supplement will be passed upon for us by Cooley LLP, San Diego, California. Davis Polk & Wardwell LLP, Menlo Park, California, is acting as counsel to the underwriters in connection with this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2023, and the effectiveness of our internal control over financial reporting as of December 31, 2023, as set forth in their reports, which are incorporated by reference in this prospectus supplement and elsewhere in the registration statement of which this prospectus supplement forms a part. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file reports, proxy statements and other information with the SEC. The SEC maintains a website that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is www.sec.gov.

Copies of certain information filed by us with the SEC are also available on our website at www.ionis.com. Information contained on, or that can be accessed through, our website is not incorporated by reference into this prospectus supplement or the accompanying prospectus.

This prospectus supplement and the accompanying prospectus are part of the registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the indenture and other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement or documents incorporated by reference in the registration statement. Statements in this prospectus about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement through the SEC's website, as provided above.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC's rules allow us to "incorporate by reference" information into this prospectus supplement and the accompanying prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus supplement and the accompanying prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in this prospectus supplement, the accompanying prospectus or a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus supplement and accompanying prospectus to the extent that a statement contained in this prospectus supplement and accompanying prospectus or a subsequently filed document incorporated by reference modifies or replaces that statement.

We incorporate by reference our documents listed below and any future filings that we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act between the date of this prospectus supplement and the termination of the offering of the securities described in this prospectus supplement. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed "filed" with the SEC, including our Compensation Committee report and performance graph or any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

This prospectus supplement and the accompanying prospectus incorporate by reference the documents set forth below that have previously been filed with the SEC:

- our Annual Report on Form 10-K for the year ended December 31, 2023, filed with the SEC on [February 21, 2024](#);
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, filed with the SEC on [May 7, 2024](#), and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, filed with the SEC on [August 1, 2024](#);
- the information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2023 from our Definitive Proxy Statement on Schedule 14A, filed with the SEC on [April 25, 2024](#);
- the description of our common stock contained in our Registration Statement on Form 8-A filed with the SEC on April 12, 1991, as updated by our Certificate of Amendment of our Restated Certificate of Incorporation filed with our [Definitive Proxy Statement on Schedule 14A](#) filed on [April 25, 2014](#), and our Certificate of Amendment of our Restated Certificate of Incorporation filed with our current report on [Form 8-K](#) filed on [December 18, 2015](#), and any amendment or report filed with the SEC for the purpose of updating the description; and
- our Current Reports on Form 8-K (other than information furnished rather than filed) filed with the SEC on [January 22, 2024](#), [February 29, 2024](#), [April 8, 2024](#), [May 31, 2024](#), [June 10, 2024](#) and [June 18, 2024](#).

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus supplement and the accompanying prospectus but not delivered with this prospectus supplement, including exhibits which are specifically incorporated by reference into such documents. You should direct any requests for documents by writing or telephoning us at the following address and telephone number:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, California 92010
(760) 931-9200
Attention: General Counsel



Common Stock

We or selling stockholders may from time to time offer and sell Common Stock in amounts, at prices and on terms described in one or more supplements to this prospectus.

This prospectus describes some of the general terms that may apply to an offering of our Common Stock. The specific terms and any other information relating to a specific offering, including the names of any selling stockholders, will be set forth in a post-effective amendment to the registration statement of which this prospectus is a part or in a supplement to this prospectus or may be set forth in one or more documents incorporated by reference in this prospectus.

Our securities may be offered and sold in the same offering or in separate offerings; to or through underwriters, dealers, and agents; or directly to purchasers. The names of any underwriter, dealer or agents involved in the sale of our securities and their compensation will be described in an applicable prospectus supplement. See “Plan of Distribution.” You should read this prospectus and the applicable prospectus supplement before you invest in our Common Stock.

Our Common Stock is currently traded on the NASDAQ Global Select Market under the symbol “IONS.”

Investing in our Common Stock involves risks.

See “[Risk Factors](#)” on page 3 of this prospectus, in the applicable prospectus supplement and similar headings in documents incorporated by reference herein and therein before investing in our Common Stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC, using the “shelf” registration process as a “well-known seasoned issuer,” as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. By using a shelf registration statement, we and any selling stockholders may offer and sell from time to time in one or more offerings the Common Stock described in this prospectus. No limit exists on the aggregate number of shares of Common Stock we and any selling stockholders may sell pursuant to the registration statement.

Neither we nor any selling stockholders or underwriters named in any prospectus supplement have authorized anyone to provide you with information different from that contained in or incorporated by reference into this prospectus or any applicable prospectus supplement. We take no responsibility for, and can provide no assurance as to the reliability of, any information that others may give you. This document may only be used where it is legal to sell these securities. You should not assume that the information contained in this prospectus, any prospectus supplement or any free writing prospectus prepared by or on behalf of us to which we have referred you, is accurate as of any date other than their respective dates regardless of the time of delivery or any sale of the Common Stock. Our business, financial condition, results of operations and prospects may have changed since that date.

This prospectus and the information incorporated herein by reference include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference in this prospectus are the property of their respective owners.

We urge you to read carefully both this prospectus and any prospectus supplement accompanying this prospectus, together with the information incorporated herein by reference as described under the heading “Where You Can Find More Information,” before deciding whether to invest in any of the securities being offered.

PROSPECTUS SUMMARY

The following summary does not contain all of the information that may be important to purchasers of our securities. Prospective purchasers of securities should carefully review the detailed information and financial statements, including the notes thereto, appearing elsewhere in or incorporated by reference into this prospectus and any prospectus supplement.

We were founded over 30 years ago to deliver innovative medicines for diseases with great medical need. Today, we are building on our advancements in RNA-targeted therapeutics to deliver our medicines to the market that have the potential to transform the lives of people with devastating diseases.

We maintain a website at www.ionispharma.com. The reference to our website does not constitute incorporation by reference into this prospectus of any of the information contained on or accessible through our website.

Our principal executive offices are located at 2855 Gazelle Court, Carlsbad, CA 92010, and our telephone number is (760) 931-9200. 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 from Isis Pharmaceuticals, Inc. to Ionis Pharmaceuticals, Inc.

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

“Ionis,” the Ionis logo, and other trademarks or service marks of Ionis Pharmaceuticals, Inc. appearing in this prospectus 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.

SPINRAZA® is a trademark of Biogen, Inc.

RISK FACTORS

Investing in our securities involves risks. Please see the risk factors described under the caption “Risk Factors” in our most recent Annual Report on Form 10-K filed with the SEC, our most recent Quarterly Report on Form 10-Q filed with the SEC, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference in this prospectus and in any accompanying prospectus supplement. Before making an investment decision, you should carefully consider these risks as well as information we include or incorporate by reference in this prospectus and in any accompanying prospectus supplement. The risks and uncertainties we have described are not the only ones that we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our business or operations.

FORWARD-LOOKING STATEMENTS

This prospectus, each prospectus supplement and the documents incorporated herein and therein by reference contain forward-looking statements regarding our business and the therapeutic and commercial potential of QALSODY (tofersen), SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen), eplontersen, olezarsen, donidalorsen, zilganersen, ulefnersen, pelacarsen, bepirovirsen, IONIS-FB-L_{RX}, and our technologies and our other products in development. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including but not limited to those related to our commercial products and the medicines in our pipeline, 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 our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements.

We claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 for all forward-looking statements.

USE OF PROCEEDS

Unless otherwise indicated in an applicable prospectus supplement, we will use the net proceeds from the sale of any securities by us for general corporate purposes and to fund our capital expenditures and working capital requirements. Pending the application of the net proceeds, we intend to invest the net proceeds in investment-grade, interest-bearing securities. We will not receive any of the proceeds from the sale of shares of our Common Stock by selling stockholders, if any, pursuant to this prospectus.

SELLING STOCKHOLDERS

If the registration statement of which this prospectus is a part is used by any selling stockholder for the resale of any shares of Common Stock registered thereunder, information about such selling stockholder, its beneficial ownership of our securities and its relationship with us will be set forth in a post-effective amendment to the registration statement, in a supplement to this prospectus, or in one or more documents incorporated by reference in this prospectus or the applicable prospectus supplement.

PLAN OF DISTRIBUTION

We or selling stockholders may sell the offered securities in one or more of the following ways, or any manner specified in a prospectus supplement:

- to or through an underwriter or underwriters;
- through dealers;
- through agents;
- directly to one or more purchasers, including affiliates of ours; or
- through a combination of any of these methods of sale.

The applicable prospectus supplement will contain the terms of the offerings of any securities. The public offering price and any discount or concessions allowed or reallocated to dealers may be changed from time to time. The applicable prospectus supplement will contain the expected time of delivery of the securities for which this prospectus is delivered.

Unless otherwise indicated in the applicable prospectus supplement, if underwriters are used in the sale of the securities, the underwriting agreement will provide that the obligations of the underwriters are subject to certain conditions precedent and that the underwriters will be obligated to purchase all of the securities if any are purchased. In connection with the sale of securities, underwriters may receive compensation from us, selling stockholders or purchasers of securities for whom they may act as agents in the form of discounts, concessions or commissions. Underwriters may sell securities to or through dealers, and dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they may act as agent.

Underwriters, agents or dealers participating in the distribution of securities may be deemed to be underwriters, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions under the Securities Act. The securities may be sold in one or more transactions either at a fixed price or at prices which may be changed based on market prices prevailing at the time of sale, at prices related to the prevailing market prices or at negotiated prices. Any underwriter, dealer or agent will be acting on a best-efforts basis or, if indicated in the applicable prospectus supplement, on a firm commitment basis.

We or selling stockholders may indemnify the underwriters, agents or dealers who participate in the distribution of securities against certain liabilities, including liabilities under the Securities Act. We or selling stockholders may also contribute to payments that the underwriters, dealers or agents or any of their controlling persons may be required to make in respect of such liabilities. Underwriters, agents or dealers may be customers of, engage in transactions with or perform services for us or our subsidiaries or selling stockholders or their affiliates in the ordinary course of business.

If so indicated in a prospectus supplement, we or selling stockholders will authorize underwriters, dealers and agents to solicit offers by certain institutions to purchase securities from us or such selling stockholders pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. These contracts will be subject only to those conditions contained in the prospectus supplement. The prospectus supplement will also contain the commission payable for solicitation of any of these contracts.

Offers to purchase securities may be solicited directly by us or selling stockholders and sales of securities may be made by us or selling stockholders directly to institutional investors or others who may be deemed to be underwriters within the meaning of the Securities Act, with respect to any resale of the securities. The terms of any such sales will be described in the prospectus supplement relating to the securities. Except as contained in the applicable prospectus supplement, no director, officer or employee of ours will solicit or receive a commission in connection with the direct sales by us of the securities, although these persons may respond to inquiries by potential purchasers and perform ministerial and clerical work in connection with any such direct sales.

DESCRIPTION OF CAPITAL STOCK

Our authorized capital stock consists of:

- 300,000,000 shares of Common Stock, of which 143,472,119 shares were outstanding as of October 31, 2023; and
- 15,000,000 shares of preferred stock, none of which were outstanding as of October 31, 2023.

Preferred Stock

Blank Check Preferred Stock

We are authorized to issue up to 15,000,000 shares of “blank check” preferred stock. 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.

Series C Junior Participating Preferred Stock

Series C Junior Participating Preferred Stock have been designated but are not outstanding. Each one one-hundredth of a share of the Series C Preferred Stock has designations and powers, preferences and rights, and qualifications, limitations and restrictions that make its value approximately equal to the value of a share of our Common Stock.

Common Stock

As of October 31, 2023, we had 300,000,000 shares of Common Stock authorized, of which 143,472,119 were issued and outstanding. As of October 31, 2023, total common shares reserved for future issuance upon the exercise or conversion of outstanding securities that are exercisable or convertible into shares of our Common Stock was approximately 74,549,442, including up to 10,701,900, 10,936,052 and 6,590,028 shares issuable upon conversion of our 1.75% convertible senior notes due 2028, our 0% convertible senior notes due 2026 (the “**2026 Notes**”) and our 0.125% convertible senior notes due 2024 (the “**2024 Notes**”), respectively. In connection with the issuance of the 2026 Notes and 2024 Notes, we entered into certain convertible note hedge transactions covering 10,936,052 and 6,590,028 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, 6,055,646 shares are reserved for issuance upon conversion of 2024 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 2024 Notes held in treasury, we expect we would receive up to 6,055,646 shares upon settlement of related convertible note hedges (without any additional dilution caused by the conversion of the 2024 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 2026 Notes and the 2024 Notes.

Voting Rights

Holders of Common Stock are entitled to one vote per share on all matters to be voted upon by the stockholders, including the election of directors. Our Common Stock does not have cumulative voting rights.

Dividend Rights

Subject to the preferential rights of outstanding shares of preferred stock, if any, the holders of Common Stock are entitled to receive dividends out of assets legally available at the times and in the amounts that our Board of Directors may determine from time to time in its discretion.

No Preemptive or Redemption Rights; Right to Receive Liquidation Distributions

Our Common Stock is not entitled to preemptive rights and is not subject to redemption or sinking fund provisions. Upon our liquidation, dissolution or winding-up, the holders of Common Stock are entitled to share equally in all of our assets remaining after payment of all liabilities and the liquidation preferences of any outstanding preferred stock.

Classified Board of Directors

Our Certificate of Incorporation provides for classified terms for the members of our Board of Directors. The Board of Directors is divided into three classes, and each class serves a three-year term. Presently, the Board has nine members.

Size of the Board of Directors; Removal of Directors; Vacancies

Our Certificate of Incorporation and Bylaws authorize our Board of Directors to fix the number of directors from time to time without stockholder approval. The Board of Directors currently consists of nine members. Directors may be removed with cause by a majority of the outstanding shares entitled to vote or without cause upon the approval of at least 66-2/3% of the outstanding shares entitled to vote. All vacancies on the Board of Directors are to be filled by the directors then in office.

Liquidation, Dissolution or Winding Up

Subject to the preferential rights of outstanding shares of preferred stock, if any, holders of Common Stock will share equally in all assets legally available for distribution, after payment of all liabilities, to our stockholders in the event of liquidation, dissolution or winding up of the Company.

Other Rights and Preferences

Our Common Stock has no sinking fund or redemption provisions or preemptive, conversion or exchange rights.

Power to Call Special Stockholder Meetings; Stockholder Action by Written Consent; Advance Notice of Stockholder Business and Nominees

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. Only our Board of Directors, Chairman of the Board or Chief Executive Officer can call special meetings of our stockholders. In addition, our Certificate of Incorporation and Bylaws require advance notice for nominations for election to our Board of Directors or for proposing matters that can be acted upon by stockholders at a stockholder meeting.

Amendment of Bylaws

Our Board of Directors is authorized to adopt, alter or repeal our Bylaws, while our Bylaws may be adopted, amended or repealed by stockholders only through the approval of at least 66-2/3% of the outstanding shares entitled to vote.

Anti-Takeover Effects of Delaware Law

We are subject to Section 203 of the Delaware General Corporation Law (“*DGCL*”), which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, unless:

- the transaction is approved by the Board of Directors before the date the interested stockholder attained that status;

- upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced; or
- on or after the date the business combination is approved by the Board and authorized at a meeting of stockholders by at least 66-2/3% of the outstanding voting stock that is not owned by the interested stockholder.

A “business combination” is defined to include any merger or consolidation involving a corporation and the interested stockholder; any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation; subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder; and the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, an “interested stockholder” is an entity or person who, together with affiliates and associates, owns (or within three years prior to the determination of interested stockholder status, did own) 15% or more of a corporation’s voting stock.

The fair price provision and Section 203 of the DGCL could prohibit or delay mergers or other takeover or change in control attempts with respect to us and, accordingly, may discourage attempts to acquire us even though such a transaction may offer our stockholders the opportunity to sell their stock at a price above the prevailing market price.

Anti-Takeover Effects of Our Certificate of Incorporation and Bylaws

Our Certificate of Incorporation includes a provision that requires at least 66-2/3% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15 percent or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Provisions of our Certificate of Incorporation and Bylaws may delay or discourage transactions involving an actual or potential change in our control or change in our management, including transactions in which stockholders might otherwise receive a premium for their shares or transactions that our stockholders might otherwise deem to be in their best interests. Therefore, these provisions could adversely affect the price of our Common Stock.

Among other things, our Certificate of Incorporation and Bylaws:

- permit our Board of Directors to issue up to 15,000,000 shares of preferred stock, with any rights, preferences and privileges as they may designate;
- provide that the authorized number of directors shall be fixed exclusively by the Board of Directors;
- provide that the Board of Directors or any individual director may only be removed with cause by the affirmative vote of the holders of at least a majority of the outstanding Common Stock or without cause by the affirmative vote of the holders of at least 66-2/3% of the voting power of all of our then outstanding Common Stock;
- provide that all vacancies, including newly created directorships, may, except as otherwise required by law or subject to the rights of holders of preferred stock as designated from time to time, be filled by the affirmative vote of a majority of directors then in office, even if less than a quorum, unless the Board of Directors determines by resolution that any such vacancies or newly created directorships shall be filled by stockholders;
- classifies our Board of Directors into three classes;

- require that any action to be taken by our stockholders must be effected at a duly called annual or special meeting of stockholders and not be taken by written consent or electronic transmission;
- provide that stockholders seeking to present proposals before a meeting of stockholders or to nominate candidates for election as directors at a meeting of stockholders must provide notice in writing in a timely manner and also specify requirements as to the form and content of a stockholder's notice;
- do not provide for cumulative voting rights (therefore allowing the holders of a majority of the shares of Common Stock entitled to vote in any election of directors to elect all of the directors standing for election, if they should so choose); and
- provide that special meetings of our stockholders may be called only by the Chairman of the Board, our Chief Executive Officer or by the Board of Directors pursuant to a resolution adopted by a majority of the total number of authorized directors (whether or not there exists any vacancies).

The foregoing provisions may make it more difficult for our existing stockholders to replace our Board of Directors as well as for another party to obtain control of us by replacing our Board of Directors. Since our Board of Directors has the power to retain and discharge our officers, these provisions could also make it more difficult for existing stockholders or another party to effect a change in management. In addition, the authorization of undesignated preferred stock makes it possible for our Board of Directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change our control.

These provisions are intended to enhance the likelihood of continued stability in the composition of our Board of Directors and its policies and to discourage certain types of transactions that may involve an actual or threatened acquisition of us. These provisions are also designed to reduce our vulnerability to an unsolicited acquisition proposal and to discourage certain tactics that may be used in proxy fights. However, such provisions could have the effect of discouraging others from making tender offers for our shares and may have the effect of deterring hostile takeovers or delaying changes in our control or management. As a consequence, these provisions also may inhibit fluctuations in the market price of our stock that could result from actual or rumored takeover attempts.

Limitation of Liability and Indemnification Matters

Our Certificate of Incorporation and Bylaws include provisions to eliminate the personal liability of our directors for monetary damages resulting from breaches of their fiduciary duty to the extent permitted under Delaware law. Delaware law provides that directors of a company will not be personally liable for monetary damages for breach of their fiduciary duty as directors, except for liabilities:

- for any breach of their duty of loyalty to us or our stockholders;
- for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law;
- for unlawful payment of dividend or unlawful stock repurchase or redemption, as provided under Section 174 of the DGCL; or
- for any transaction from which the director derived an improper personal benefit.

In addition, our Bylaws provide that we will indemnify our directors and executive officers to the fullest extent not prohibited by Delaware law or any other applicable law, except that we will generally not be required to indemnify a director or executive officer in connection with any proceeding initiated by such director or executive officer. In addition, we have entered into indemnity agreements with each of our executive officers and directors and certain non-executive officers which provide, among other things, that we will indemnify such officer or director, under the circumstances and to the extent provided for therein, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or

may be made a party by reason of his or her position as a director, officer or other agent of Ionis, and otherwise to the fullest extent permitted under Delaware law and our Bylaws.

Listing

Our Common Stock is listed on the NASDAQ Global Select Market under the symbol “IONS.”

Transfer Agent and Registrar

The transfer agent and registrar for our Common Stock is Equiniti Trust Company. Its address is 1110 Centre Pointe Curve, Mendota Heights, MN 55120, and its telephone number is (800) 401-1957.

LEGAL MATTERS

The validity of the issuance of the Common Stock offered hereby will be passed upon for us by Patrick R. O'Neil, our Executive Vice President, Chief Legal Officer, General Counsel, and Corporate Secretary.

Mr. O'Neil holds or has the right to acquire shares of Ionis' Common Stock in an aggregate amount that is less than 1% of Ionis' outstanding Common Stock.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our [Annual Report on Form 10-K](#) for the year ended December 31, 2022, and the effectiveness of our internal control over financial reporting as of December 31, 2022, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements and our management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2022 are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at www.sec.gov. The documents referred to below under "Incorporation by Reference" are also available on our corporate website, www.ionispharma.com. We have not incorporated by reference into this prospectus the information on our website, and you should not consider it to be a part of this prospectus.

We have filed with the SEC a registration statement under the Securities Act relating to the offering of these securities. The registration statement, including the attached exhibits, contains additional relevant information about us and the securities. This prospectus does not contain all of the information set forth in the registration statement. You can obtain a copy of the registration statement (including the exhibits and schedules thereto), at prescribed rates, from the SEC at www.sec.gov, or our corporate website at www.ionispharma.com.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to “incorporate by reference” in this prospectus the information that we file with it. This means that we can disclose important information to you in this document by referring you to other filings we have made with the SEC. The information incorporated by reference is considered to be part of this prospectus. The information incorporated by reference in this prospectus is accurate only as of the date of the information on the front cover of the applicable document, or such earlier date as is expressly stated or otherwise apparent with respect to such incorporated information in the applicable document, regardless of the time of delivery of this prospectus or any sale of securities.

This prospectus incorporates by reference the documents listed below, which we have filed with the SEC:

- our [Annual Report on Form 10-K](#) for the fiscal year ended December 31, 2022, filed on February 22, 2023;
- portions of our [Definitive Proxy Statement on Schedule 14A](#) filed on April 20, 2023, incorporated by reference into the Annual Report on Form 10-K for our fiscal year ended December 31, 2022;
- our Quarterly Reports on Form 10-Q for the quarter ended March 31, 2023, filed on [May 3, 2023](#), the quarter ended June 30, 2023, filed on [August 9, 2023](#), and the quarter ended September 30, 2023, filed on [November 2, 2023](#);
- our Current Reports on Form 8-K filed on [January 9, 2023](#), [March 27, 2023](#), [April 24, 2023](#), [April 26, 2023](#), [June 5, 2023](#), [June 6, 2023](#), [June 12, 2023](#), [July 10, 2023](#), [August 3, 2023](#), [August 4, 2023](#), [August 22, 2023](#), [August 23, 2023](#), [September 26, 2023](#), and [September 27, 2023](#); and
- the description of our Common Stock contained in our Registration Statement on Form 8-A filed with the SEC on April 2, 1991, as updated by our Certificate of Amendment of our Restated Certificate of Incorporation filed with our [Definitive Proxy Statement on Schedule 14A](#) filed on [April 25, 2014](#), and our Certificate of Amendment of our Restated Certificate of Incorporation filed with our current report on [Form 8-K](#) filed on [December 18, 2015](#).

We incorporate by reference any additional documents that we may file with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act (other than the portions of those made pursuant to Item 2.02 or Item 7.01 of Form 8-K or other information “furnished” to the SEC) prior to the termination of the offering of the securities. These documents may include periodic reports, like Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as Proxy Statements. Any material that we subsequently file with the SEC will automatically update and replace the information previously filed with the SEC.

This prospectus may contain information that updates, modifies or is contrary to information in one or more of the documents incorporated by reference in this prospectus. You should rely only on the information incorporated by reference or provided in this prospectus. Neither we nor any selling stockholders have authorized anyone else to provide you with different information. You should not assume that the information in this prospectus is accurate as of any date other than the date of this prospectus or the date of the documents incorporated by reference in this prospectus.

We will provide to each person, including any beneficial owner, to whom this prospectus is delivered, upon written or oral request, at no cost, a copy of any and all of the information that is incorporated by reference in this prospectus.

Requests for such documents should be directed to:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, California 92010
(760) 931-9200
Attention: General Counsel

In addition, copies of our filings are available through our corporate website at www.ionispharma.com as soon as reasonably practicable after we electronically file such material with the SEC.

\$500,000,000



Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Morgan Stanley

Goldman Sachs & Co. LLC

September , 2024
