UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): September 9, 2024

IONIS PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in its Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

000-19125	**33-0336973**
(Commission File No.)	**(IRS Employer Identification No.)**

2855 Gazelle Court
Carlsbad, CA 92010
(Address of Principal Executive Offices and Zip Code)

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

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

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

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

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (Section 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (Section 240.12b-2 of this chapter).

Emerging growth company ☐

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

Item 8.01. Other Events.

On September 9, 2024, Ionis Pharmaceuticals, Inc. (or Ionis, we, us or our company) filed a preliminary prospectus supplement with the U.S. Securities and Exchange Commission, or the SEC, under its effective shelf registration statement on Form S-3 (Registration Statement No. 333-275741), or the Preliminary Prospectus Supplement, in connection with a proposed registered underwritten public offering of common stock.

The Preliminary Prospectus Supplement contains information relating to recent developments concerning Ionis' business and includes the following disclosure:

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' Pipeline[1]

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

(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.

Forward-Looking Statements

Certain statements contained in this report are forward-looking statements that involve a number of risks and uncertainties. Such forward-looking statements include, without limitation, statements regarding Ionis' expectations with respect to Ionis' business and the therapeutic and commercial potential of Ionis' marketed medicines, including SPINRAZA (nusinersen), QALSODY (tofersen), WAINUA (eplontersen), TEGSEDI (inotersen) and WAYLIVRA (volanesorsen), as well as Ionis' 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. Words such as "anticipate," "believe," "could," "continue," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "will," "would" and similar expressions are intended to identify forward-looking statements, though not all forward-looking statements necessarily contain these identifying words. For such statements, Ionis claims the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995. Actual events or results may differ materially from Ionis' expectations. Factors that could cause actual results to differ materially from the forward-looking statements include, but are not limited to, risks and uncertainties associated with market conditions, the satisfaction of customary closing conditions related to the offering, macroeconomic and geopolitical events, Ionis' commercial products and the medicines in Ionis' 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. Additional factors that could cause actual results to differ materially from those stated or implied by Ionis' forward-looking statements are disclosed in

Ionis' filings with the SEC, including in the section captioned "Risk Factors" in Ionis' most recent Annual Report on Form 10-K and subsequently filed Quarterly Reports on Form 10-Q and the Preliminary Prospectus Supplement. These forward-looking statements represent Ionis' judgment as of the time of this report. Ionis disclaims any intent or obligation to update these forward-looking statements, other than as may be required under applicable law.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

IONIS PHARMACEUTICALS, INC.

Dated: September 9, 2024

By: /s/ Patrick R. O'Neil

PATRICK R. O'NEIL
Executive Vice President, Chief Legal Officer and General Counsel