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): March 27, 2023

IONIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in 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 March 27, 2023, Ionis Pharmaceuticals, Inc. issued a press release announcing positive topline results from the 66-week analysis of the Phase 3 NEURO-TTRansform study of eplontersen in patients with hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN).

A copy of this press release is attached as Exhibit 99.1 to this Current Report and incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press Release dated March 27, 2023.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

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: March 27, 2023

By: /s/ Patrick R. O'Neil

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

Exhibit 99.1

Ionis reports positive topline 66-week results of eplontersen Phase 3 study for patients with ATTRv-PN

- *Eplontersen met co-primary endpoints demonstrating sustained reduction in TTR and benefits in neuropathy and quality of life through 66 weeks*
- *35 and 66-week data to be presented at the American Academy of Neurology (AAN) Annual Meeting in April*

CARLSBAD, Calif., March 27, 2023 – Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced positive topline results from the 66-week analysis of the Phase 3 NEURO-TTRansform study of Ionis and AstraZeneca's eplontersen in patients with hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN), a debilitating and potentially fatal disease that leads to peripheral nerve damage and motor disability.

At 66 weeks, patients treated with eplontersen continued to demonstrate a statistically significant and clinically meaningful change from baseline versus an external placebo group on the co-primary endpoints of modified Neuropathy Impairment Score +7 (mNIS+7), a measure of neuropathic disease progression, and Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN). The study also met its third co- primary endpoint demonstrating a statistically significant reduction in serum TTR concentration versus an external placebo group. TTR reductions were consistent with those reported at week 35. Eplontersen continued to demonstrate a safety and tolerability profile consistent with that observed at 35 weeks.

"The positive results from the 66-week analysis of the Phase 3 NEURO-TTRansform trial show that eplontersen provided consistent and sustained transthyretin protein reduction and that a substantial number of patients improved in measures of both neuropathy progression and quality of life," said Sami Khella, M.D., chief, department of neurology, Penn Presbyterian Medical Center and professor of clinical neurology, University of Pennsylvania School of Medicine. "This builds on the favorable 35-week results, which first demonstrated eplontersen's potential to significantly improve outcomes in this underserved population."

"These latest results from our NEURO-TTRansform study represent an important step towards delivering a potential new therapy for ATTRv-PN patients living with this debilitating and fatal disease. We are encouraged by the sustained benefit demonstrated by eplontersen and what a self-administered treatment could mean for patients and families affected by ATTRv-PN," said Eugene Schneider, M.D., executive vice president and chief clinical development officer for Ionis. "Together, with our partner AstraZeneca, we look forward to sharing detailed results from this study at the upcoming American Academy of Neurology Annual Meeting."

“These results further underscore eplontersen’s potential to be a best-in-class treatment across all forms of transthyretin-mediated amyloidosis, including polyneuropathy and cardiomyopathy which can lead to heart failure,” said Mene Pangalos, executive vice president, BioPharmaceuticals R&D, AstraZeneca. “With limited treatment options currently available, there is an urgent unmet medical need for new therapies and earlier, accurate diagnosis across the different types of this systemic, progressive and fatal condition.”

Data from both the 35 and 66-week analyses will be presented as an Emerging Science presentation at the American Academy of Neurology (AAN) Annual Meeting in April. The initial results from the 35-week analysis were presented at the International Symposium on Amyloidosis meeting in September 2022.

As part of a global development and commercialization agreement, Ionis and AstraZeneca are seeking regulatory approval for eplontersen for the treatment of ATTRv-PN in the U.S. and plan to seek regulatory approval in Europe and other parts of the world. Earlier this month, the U.S. Food and Drug Administration accepted a New Drug Application for eplontersen for the treatment of ATTRv-PN with a PDUFA action date of Dec. 22, 2023. Eplontersen was granted Orphan Drug Designation in the U.S.

Eplontersen is currently being evaluated in the Phase 3 CARDIO-TTRansform study for transthyretin amyloid cardiomyopathy (ATTR-CM), a systemic, progressive and fatal condition that typically leads to progressive heart failure and often death within three to five years from disease onset.

About the NEURO-TTRansform Study

NEURO-TTRansform is a global, open-label, randomized trial evaluating the efficacy and safety of eplontersen in patients with ATTRv-PN. The trial enrolled adult patients with ATTRv-PN Stage 1 or Stage 2 and up to week 66 eplontersen is being compared to the external placebo group from the NEURO-TTR registrational trial for inotersen that Ionis completed in 2017. The final analysis comparing eplontersen to external placebo was completed at week 66 and all patients will be followed on treatment until week 85, when they will have the option to transition into an open-label extension study. For more information on the NEURO-TTRansform study, please visit: https://clinicaltrials.gov/ct2/show/NCT04136184

About Hereditary Transthyretin-Mediated Amyloid Polyneuropathy (ATTRv-PN)

Hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN) is caused by the accumulation of misfolded mutated TTR protein in the peripheral nerves. Patients with ATTRv-PN experience ongoing debilitating nerve damage throughout their body resulting in the progressive loss of motor functions, such as walking. These patients also accumulate TTR in other major organs, which progressively compromises their function. The damage from misfolded TTR protein accumulation leads to disability within five years of diagnosis and is generally fatal within a decade.

About Eplontersen

Eplontersen is an investigational **LI**gand-**C**onjugated **A**ntisense (LICA) medicine designed to inhibit the production of TTR protein. Eplontersen is being developed as a monthly self-administered subcutaneous injection to treat all types of ATTR. ATTR amyloidosis is a systemic, progressive and fatal disease in which patients experience multiple overlapping clinical manifestations caused by the inappropriate formation and aggregation of TTR amyloid deposits in various tissues and organs, including peripheral nerves, heart, intestinal tract, eyes, kidneys, central nervous system, thyroid and bone marrow. The progressive accumulation of TTR amyloid deposits in these tissues and organs leads to organ failure and eventually death.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been a leader in RNA-targeted therapy, pioneering new markets and changing standards of care with its novel antisense technology. Ionis currently has three marketed medicines and a promising late-stage pipeline highlighted by cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision to become the leader in genetic medicine, utilizing a multi-platform approach to discover, develop and deliver life-transforming therapies.

To learn more about Ionis visit www.ionispharma.com and follow us on Twitter @ionispharma.

Ionis' Forward-looking Statements

This press release includes forward-looking statements regarding Ionis' business and the therapeutic and commercial potential of Ionis' technologies, eplontersen and other products in development. Any statement describing Ionis' 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. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements.

Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended Dec. 31, 2022, which is on file with the Securities and Exchange Commission. Copies of this and other documents are available from the Company.

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

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