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): July 10, 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 July 10, 2023, Ionis Pharmaceuticals, Inc. issued a press release announcing positive topline 85-week data from the Phase 3 NEURO-TTRansform study 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 July 10, 2023.
99.2	Overview of key results from the Phase 3 NEURO-TTRansform 85-week topline analysis.
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: July 10, 2023

By: /s/ Patrick R. O'Neil

PATRICK R. O'NEIL

Executive Vice President, Chief Legal Officer and General Counsel

Exhibit 99.1

Eplontersen continued to show improvement in ATTRv-PN through 85 weeks

- *Topline Phase 3 NEURO-TTRansform results show eplontersen continued to halt neuropathy disease progression and improve quality of life through 85 weeks*
- *Data further strengthen eplontersen's differentiated profile, positioning it to be an important potential treatment for patients with ATTRv-PN*

CARLSBAD, Calif., July 10, 2023 – Ionis Pharmaceuticals (Nasdaq: IONS) today announced positive topline, 85-week data from the Phase 3 NEURO-TTRansform study in patients with hereditary transthyretin-mediated amyloid polyneuropathy (ATTRv-PN). Ionis and AstraZeneca's eplontersen continued to show sustained improvements in measures of neuropathy disease and a favorable safety and tolerability profile.

An overview of key results from the 85-week topline analysis is available here. At 85 weeks, eplontersen continued to show a sustained reduction in serum TTR concentration compared to baseline and continued to halt disease progression as measured by the modified Neuropathy Impairment Score +7 (mNIS+7). Eplontersen also showed continued improvement on the Norfolk Quality of Life Questionnaire-Diabetic Neuropathy (Norfolk QoL-DN) compared to baseline. Results from the NEURO-TTRansform primary analysis at 66 weeks were presented earlier this year.

"These positive findings further strengthen eplontersen's efficacy and safety profile, underscoring its potential to be an important, differentiated advancement for patients with this progressive, debilitating and fatal disease," said Eugene Schneider, M.D., Ionis' executive vice president and chief clinical development officer. "A substantial number of eplontersen-treated patients showed improvement in neuropathy impairment and quality of life through 19 months of treatment. ATTRv-PN continues to be an underserved patient population and we look forward to working with regulatory authorities to bring this important new, self-administered treatment to patients."

Results from the 85-week exploratory analysis of NEURO-TTRansform will be submitted for presentation at an upcoming medical meeting. 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. The U.S. Food and Drug Administration accepted the 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-mediated 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 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 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 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 at week 35, week 66 and week 85. The final analysis comparing eplontersen to an external placebo group was completed at week 66. All patients were then followed on treatment until week 85 and evaluated four weeks after the last dose in an end-of-trial assessment. Following treatment and the end-of-trial assessments, patients were eligible to enter an open-label extension study to continue receiving eplontersen once every four weeks or enter a 20-week post-treatment evaluation period. For more information on the NEURO-TTRansform study, please visit: https://clinicaltrials.gov/ct2/show/NCT04136184

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. Ionis currently has four 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 eplontersen, Ionis' technologies 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 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, and the most recent Form 10-Q quarterly filing, which are on file with the Securities and Exchange Commission. Copies of these and other documents are available from the Company.

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

Ionis Investor Contact:
D. Wade Walke, Ph.D.
info@ionisph.com
760-603-2331

Ionis Media Contact:
Sophia Patel
ionis_ca@ionisph.com
760-603-4679

Exhibit 99.2

Eplontersen: NEURO-TTRansform Week 85 Topline Results

July 10, 2023

Nasdaq: IONS

Forward-Looking Statements

This presentation includes forward-looking statements regarding our business and the therapeutic and commercial potential of eplontersen, and Ionis' technologies. 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 our Form 10-K for the year ended December 31, 2022, and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available at www.ionispharma.com.

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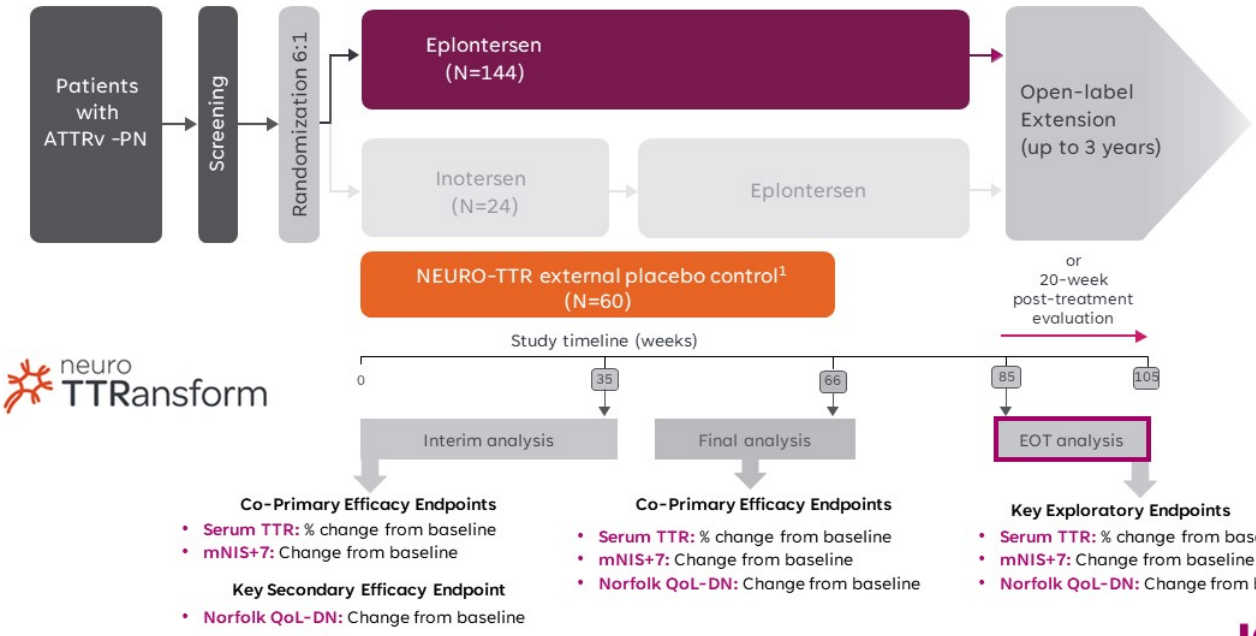
NEURO-TTRansform Study Designed to Demonstrate Benefit in Patients with ATTRv-PN

- A multicenter, open-label study in 168 patients with hereditary TTR amyloid polyneuropathy (ATTRv-PN)



[1]Benson et al, *N Engl J Med* (2018) 379:22-3 1. Figure adapted from Coelho et al, *Neurol Ther* (2021) 10:375-89.

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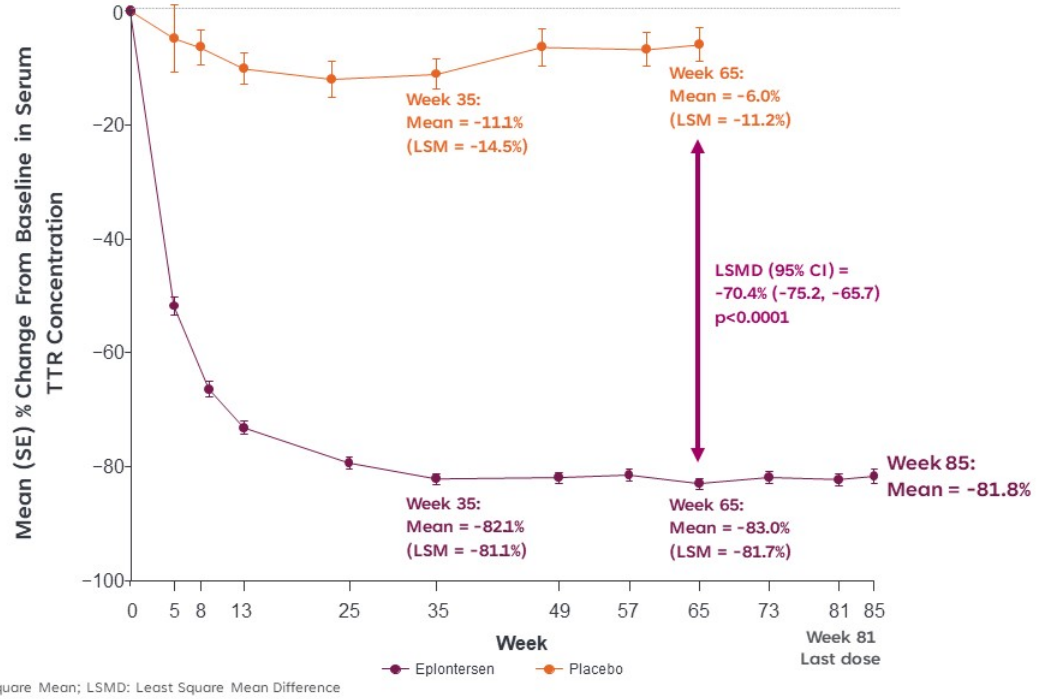
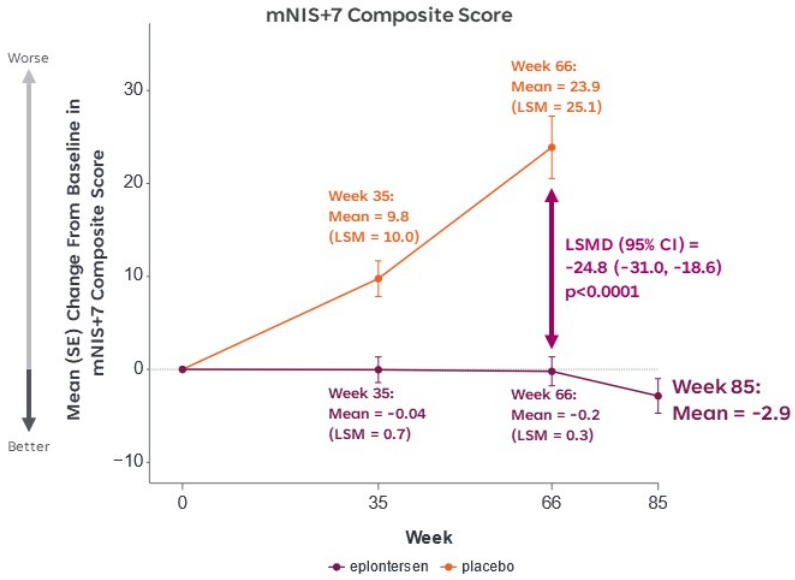
Eplontersen Treatment Resulted in Substantial and Sustained Reductions in Serum TTR Concentration Compared to Baseline



LSM: Least Square Mean; LSMD: Least Square Mean Difference

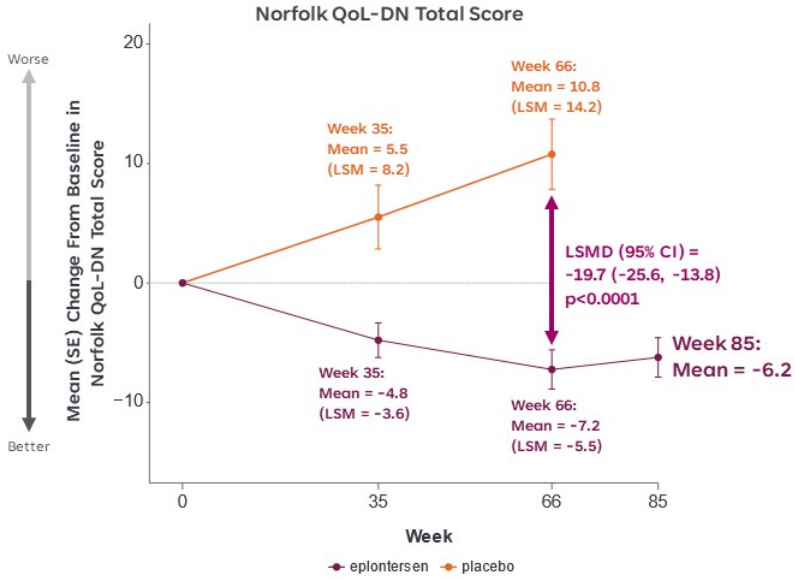
Eplontersen Continued to Halt Neuropathy Progression at Week 85



- Substantial number of patients showed improvement in neuropathy impairment through 19 months of treatment

LSM: Least Square Mean; LSMD: Least Square Mean Difference

Eplontersen Continued to Improve Quality of Life at Week 85



- Substantial number of patients showed improvement in quality of life through 19 months of treatment

LSM: Least Square Mean; LSMD: Least Square Mean Difference

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Eplontersen Continued to Demonstrate a Favorable Safety and Tolerability Profile at 85 Weeks[1]

- At 85 weeks, TEAEs incidence remains consistent with week 66
- No TEAEs of special interest led to study drug discontinuation
- No imbalance of ocular events excluding vitamin A decrease or deficiency
- No SAEs were related to study drug
- 3 non-drug related deaths in the eplontersen group, all related to known sequelae of ATTR amyloidosis[2-6]

Incidence, n (%)	Placebo	Eplontersen Week 66	Eplontersen Week 85
N	60	144	144
Any TEAE	60 (100)	140 (97.2)	141 (97.9)
Related to study drug	23 (38.3)	53 (36.8)	55 (38.2)
Leading to study drug discontinuation	2 (3.3)	6 (4.2)	8 (5.6)
TEAE of special interest	14 (23.3)	41 (28.5)	43 (29.9)
Ocular events potentially related to Vit A deficiency	12 (20.0)	39 (27.1)	41 (28.5)
Ocular events excluding lab TEAEs of Vit A decrease or deficiency	9 (15.0)	24 (16.7)	26 (18.1)
Thrombocytopenia	1 (1.7)	3 (2.1)	3 (2.1)
Glomerulonephritis	2 (3.3)	0	0
Other TEAE of interest	48 (80.0)	87 (60.4)	93 (64.6)
Any serious TEAE	13 (21.7)	21 (14.6)	27 (18.8)
Related to study drug	1 (1.7)	0	0
Fatal TEAE	0	2 (1.4)	3 (2.1)
Related to study drug	0	0	0

[1]External placebo concluded at week 66 while eplontersen patients remained on treatment and could accrue additional events; [2]Cavallaro et al, *Neurology* (2016) 87:750-1; [3]Yamada et al, *Prog Mol Biol Transl Sci* (2012) 107:41-78; [4]Yamashita et al, *Neurology* (2008) 70:123-28; [5]Ellie et al, *Neurology* (2001) 57:135-7; [6]Porcari et al, *Cardiovasc Res* (2023) 118:3517-35.

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