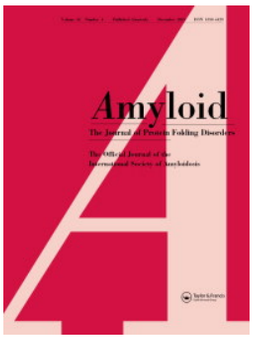

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Amyloid
The Journal of Protein Folding Disorders

ISSN: 1350-6129 (Print) 1744-2818 (Online) Journal homepage: www.tandfonline.com/journals/iamy20

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To cite this article: Jonas Wixner, Isabel Conceição, John L. Berk, David Adams, Michael J. Polydefkis, Shahram Attarian, Julian D. Gillmore, P. James B. Dyck, Jersey Chen, T. Jesse Kwoh, Jonatan Nåtman, Wunan Zhou & Márcia Waddington Cruz (28 Oct 2025): Neuropathy impairment and nutritional status with eplontersen in patients with hereditary transthyretin-mediated amyloidosis, Amyloid, DOI: 10.1080/13506129.2025.2577361

To link to this article: https://doi.org/10.1080/13506129.2025.2577361

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https://doi.org/10.1080/13506129.2025.2577361

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LETTER TO THE EDITOR

Neuropathy impairment and nutritional status with eplontersen in patients with hereditary transthyretin-mediated amyloidosis

Gastrointestinal disturbances are experienced by more than half of patients with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN), with potentially serious complications that may include weight loss, severe chronic diarrhea, and cachexia, with a consequent negative impact on overall nutritional status, quality of life (QoL), and reduced survival [1–3].

There is a need for more evidence to characterize the impact of pharmacological treatments in patients with ATTRv-PN, particularly those with worsening nutritional status. This may be evaluated by modified body mass index (mBMI), where mBMI <600 kg/m^2 × serum albumin [g/L]) has been shown to be a marker of poor prognosis in these patients [1,4]. Use of mBMI avoids potential discrepancies in conventional BMI measurement due to low serum albumin level and fluid retention, and thus, better reflects overall nutritional health [1,3,4].

Eplontersen is approved in multiple countries for use in adults with ATTRv-PN. In the phase 3 NEURO-TTRansform trial evaluating eplontersen vs. historical placebo in adults with ATTRv-PN, eplontersen demonstrated reduced serum transthyretin (TTR), halted progression of neuropathy impairment, and improved QoL, with no notable deterioration in nutritional status [5].

This secondary analysis from NEURO-TTRansform evaluated whether the benefits of eplontersen on neuropathy impairment and patient QoL are maintained, irrespective of nutritional status change.

The design and methods of NEURO-TTRansform (NCT04136184) have been published in detail [5], with inclusion criteria and endpoints similar to those of the phase 3 NEURO-TTR study (NCT01737398) of inotersen vs. placebo [6].

It was hypothesized that mBMI changes would correlate with and predict changes in modified Neuropathy Impairment Score + 7 (mNIS + 7) composite score and Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) total score. These outcomes at Week 66 were compared for the continuous eplontersen group from NEURO-TTRansform and the historical placebo group from NEURO-TTR. Patients were categorized according to change from baseline to Week 65 in mBMI (BMI [kg/m^2] × serum albumin [g/L]); >10% decrease, <2.5%–10% decrease, −2.5%–+2.5% change, >2.5%–10% increase, or >10% increase (where lower values indicate poorer nutritional status).

This analysis included all randomized NEURO-TTRansform participants who received ≥1 dose of eplontersen. Patients could have ATTRv-PN with mixed phenotype features, including cardiomyopathy (CM).

The effects of eplontersen on neuropathy impairment and QoL were assessed by mBMI category as change from baseline to Week 66 in mNIS + 7 composite score and Norfolk QoL-DN total score. Higher scores indicate poorer function; a decrease indicates improvement [5,6]. Subgroup assessment by those with and without CM was performed for both neuropathy impairment and QoL.

The efficacy analysis population included 144 patients who received continuous eplontersen, and 60 patients who received historical placebo. Baseline characteristics of participants have been reported previously [5]. Patients in the eplontersen group had longer disease duration, and were more likely to have received treatment with TTR stabilizers vs. the historical placebo group. These trends were consistent across mBMI categories between subgroups, including across CM and non-CM subgroups, particularly the CM group (Table S1).

Mean change in mBMI from baseline was minimal with eplontersen throughout the study; by contrast, historical placebo showed marked worsening over time (Figure 1A).

Change from baseline in mNIS + 7 composite score during eplontersen treatment was minimal across mBMI categories and remained stable even with worsening nutritional status (Figure 1B). By contrast, mNIS + 7 consistently worsened with historical placebo, with the greatest increase in those with

Supplemental data for this article can be accessed online at https://doi.org/10.1080/13506129.2025.2577361.

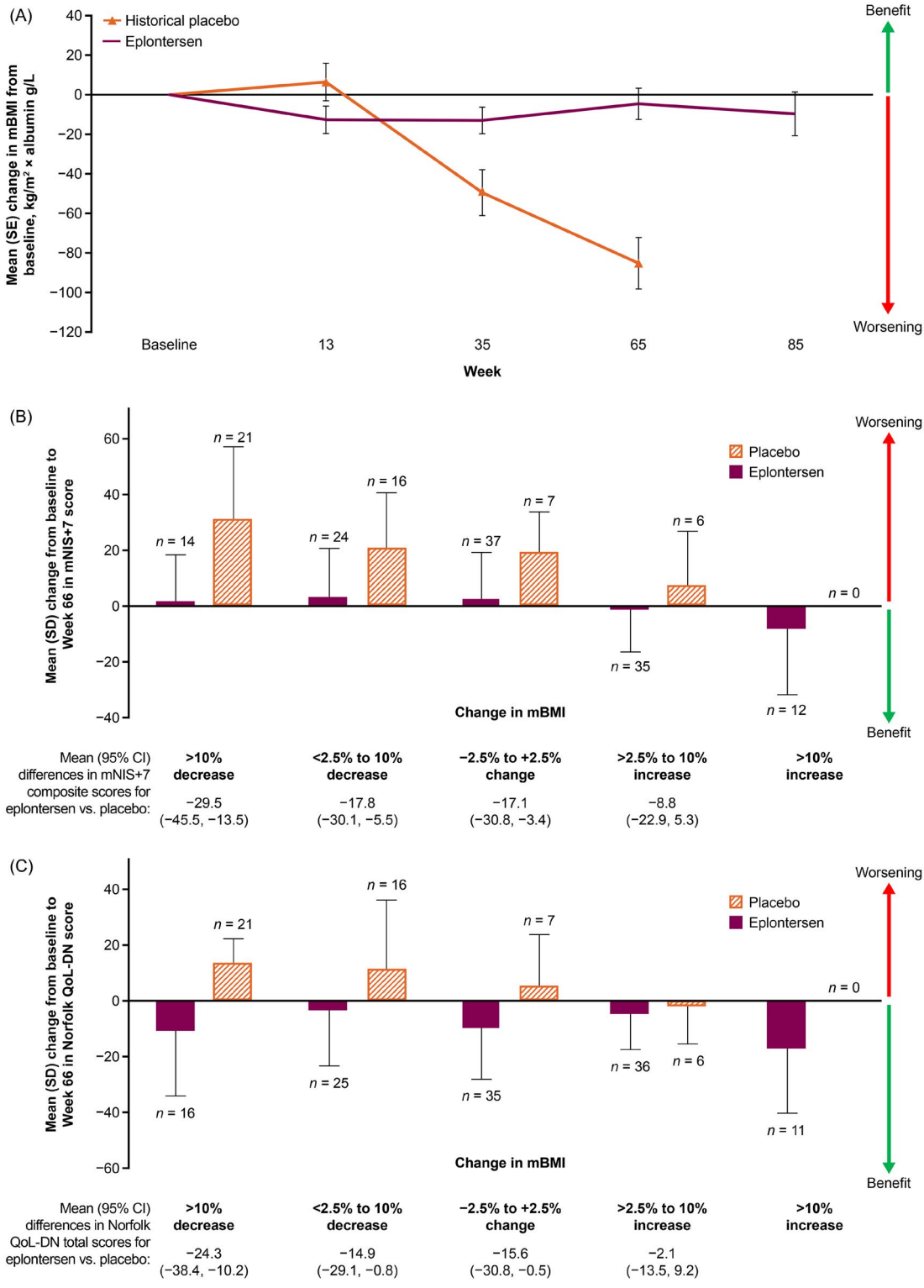

Figure 1. (A) Mean (SE) change in mBMI from baseline. (B) Mean change from baseline to Week 66 in mNIS + 7 composite score by category of change in mBMI to Week 65. (C) Mean change from baseline to Week 66 in Norfolk QoL-DN total score by category of change in mBMI to Week 65. (A) Historical placebo from the NEURO-TTR trial [6]. (B) Category of change in mBMI from baseline at Week 65. Higher mNIS + 7 composite score indicates a poorer health status. Data were missing at baseline or at Week 65 for 14 patients in the eplontersen group and 8 patients in the placebo group. Historical placebo from the NEURO-TTR trial [6]; no patients in this group had a >10% increase in mBMI. (C) Category of change in mBMI from baseline at Week 65. Higher Norfolk QoL-DN score indicates a poorer health status. Data were missing at baseline or at Week 65 for 14 patients in the eplontersen group and 8 patients in the placebo group. Historical placebo from the NEURO-TTR trial [6]; no patients in this group had a >10% increase in mBMI. CI: confidence interval; mBMI: modified body mass index; mNIS + 7: modified Neuropathy Impairment Score +7; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; SD: standard deviation; SE: standard error.

worsening nutritional status. The correlation between change in mNIS + 7 and percent change in mBMI was low with a Pearson correlation coefficient r = −0.381 overall, r = −0.165 with eplontersen (p=.069), and r = −0.352 with historical placebo (p=.012) (Figure S1A). Regardless of CM status, eplontersen demonstrated consistent benefit in neuropathy impairment across mBMI categories vs. historical placebo. Mean difference (95% confidence interval [CI]) in change from baseline in mNIS + 7 for eplontersen vs. historical placebo at Week 66 was comparable in CM (−22.2 [−32.0, −12.4] and non-CM (−24.9 [−33.9, −15.9]) subgroups.

Across mBMI categories, eplontersen demonstrated consistent improvements in Norfolk QoL-DN vs. the QoL values observed in the historical placebo group (Figure 1C). There was no significant correlation between change in Norfolk QoL-DN total score, and percent change in mBMI (overall r = of −0.258); r = −0.050 with eplontersen (p=.581); however, this was significant with historical placebo (r = −0.294; p=.038) (Figure S1B). Regardless of CM status, eplontersen demonstrated consistent benefit in patient QoL across mBMI categories vs. historical placebo. Mean (95% CI) difference in change from baseline in Norfolk QoL-DN at Week 66 was comparable in CM (−14.9 [−25.1, −4.6] and non-CM (−20.0 [−28.3, −11.8]) subgroups.

The findings from this secondary analysis of NEURO-TTRansform in patients with ATTRv-PN suggest that the benefits of eplontersen on neuropathy impairment and QoL are not associated with nutritional status, and that eplontersen continues to provide benefit in patients with worsening nutritional status. In the group with the greatest decline in nutritional status, neuropathy impairment and QoL remained stable or improved with eplontersen, while the historical placebo group showed consistent worsening. Findings were also generally consistent across CM and non-CM subgroups, indicating treatment impact for patients with ATTRv-PN, including those with mixed phenotypes.

Gastrointestinal complications, such as unintentional weight loss, are frequently observed in patients with ATTRv-PN, especially those diagnosed <50 years of age and those with the Val30Met (p.Val50Met) variant [1,2]. These may increase in prevalence over time alongside increasing disease duration, and the impact of worsening nutritional status may be exacerbated with delayed investigation and suboptimal treatment [2]. Current management of gastrointestinal disturbances in patients with ATTRv-PN include the use of supportive care, dietary changes, and pharmacological agents [7]. Although monitoring changes, symptoms, and treatment response typically involves nutritional status assessment in clinical practice [8], impacts may be subclinical and under-recognized [2].

Despite mBMI being a recognized and robust index of nutritional status in patients with ATTRv-PN [2], in the current study, there was a weak correlation between nutritional status and mNIS + 7 and Norfolk QoL-DN score changes. This suggests that weight loss is only modestly associated with neuropathy impairment and QoL decline, thus affecting the interpretation of mBMI as a disease progression marker. This finding suggests that the impact of ATTRv-PN on autonomic dysfunction in the gastrointestinal tract is largely independent from mNIS + 7 and Norfolk QoL-DN score assessment, likely because determination of severity of autonomic dysfunction is a small part of mNIS + 7 and Norfolk scoring systems. Notably, a weak but significant correlation was observed between mBMI and EuroQol 5-Dimension index score (r^2 = 0.217; p<.001) as part of a gastrointestinal symptoms analysis involving >1700 patients with ATTR amyloidosis from the Transthyretin Amyloidosis Outcomes Survey (THAOS) registry [1]. Although it was not possible to determine the impact of pharmacological treatment on outcomes in THAOS [1], an analysis of patients with Val30Met ATTRv-PN demonstrated improvements in mBMI that coincided with less deterioration in neurologic function and better-preserved QoL, with tafamidis vs. placebo [9].

Different ATTRv-PN variants are known to have varying affinity for motor, sensory, or autonomic nerves [10,11], and further research into patients with dominant autonomic dysfunction is warranted to determine whether these individuals represent a specific subset with a suboptimal response to eplontersen.

In conclusion, in this secondary analysis of patients with ATTRv-PN from NEURO-TTRansform, eplontersen halted progression of neuropathy impairment and improved QoL, whilst these outcomes worsened in the historical placebo group, regardless of degree of change in nutritional status from baseline, including in patients with worsening nutritional status. Thus, even in cases of dramatic weight loss and nutritional decline, eplontersen can provide benefit.

Acknowledgments

The authors would like to thank the patients, their families, caregivers, and all investigators involved in the NEURO-TTRansform trial, and Ionis Pharmaceuticals, Inc. (Carlsbad, CA, USA) and AstraZeneca for their participation and/or contribution. This study was sponsored by AstraZeneca and Ionis Pharmaceuticals, Inc. The sponsors were involved in the study design and collection, analysis,

and interpretation of data, as well as data checking of information provided in the manuscript. Ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors. Medical writing support, including assisting authors with development of the initial draft and incorporation of comments was provided by Carl V. Felton, PhD, CMPP, and editorial support and submission by Jess Fawcett, BSc, of Core (a division of Prime, London, UK), supported by AstraZeneca according to Good Publication Practice guidelines (Link).

Author contributions

All authors contributed to the study conception, design, and development/review of the first draft and subsequent versions of the manuscript. All authors read and approved the final manuscript. Material preparation, data collection, and analysis were performed by Jersey Chen, T. Jesse Kwoh, and Jonatan Nåtman.

Disclosure statement

JW is a consultant to Akcea, AstraZeneca, Alnylam, Bayer, Pfizer, and Intellia. IC has received financial support as the primary investigator and consultant to Pfizer, Alnylam, Ionis Pharmaceuticals, Inc., and AstraZeneca. JLB has participated in an Ionis *ad hoc* advisory committee and is a consultant to Intellia and Alnylam. DA is a consultant to AstraZeneca, Alnylam, and BridgeBio. MJP is a consultant to Alnylam, AstraZeneca, and Intellia, and was a principal investigator for the NEURO-TTR trial. SA has provided consultancy for Alnylam, AstraZeneca, and Pfizer. JDG is a consultant to Alnylam, AstraZeneca, ATTRalus, BridgeBio, Ionis Pharmaceuticals, Inc., Intellia, and Pfizer. PJBD has nothing to disclose. JC, JN, and WZ are employees of, and hold stock in, AstraZeneca. TJK was an employee of Ionis Pharmaceuticals, Inc. at the time the study was performed, and is currently contracted at Ionis Pharmaceuticals, Inc. MWC is a principal investigator for the NEURO-TTRansform trial and is a consultant for Ionis Pharmaceuticals, Inc.

Data availability statement

Data requests from qualified researchers will be considered once all three of the following criteria are met: (1) 12 months from marketing approval of the study drug in both the United States and European Union; (2) 18 months from conclusion of the study; and (3) 6 months from the publication of this article. For additional information, visit https://vivli.org/ourmembers/ionis.

Funding

The NEURO-TTRansform trial was sponsored by Ionis Pharmaceuticals, Inc. The analyses presented here were supported by AstraZeneca.

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Received 3 September 2025; revised 10 October 2025; accepted 14 October 2025