**Title**: Eplontersen for Hereditary TransthyretinAmyloidosis With Polyneuropathy

**Authors**: Teresa Coelho,MD, PhD; Wilson Marques Jr, MD, PhD; Noel R. Dasgupta, MD; Chi-Chao Chao,MD, PhD; Yeşim Parman, MD; Marcondes Cavalcante França Jr,MD, PhD; Yuh-Cherng Guo, MD; Jonas Wixner,MD, PhD; Long-Sun Ro, PhD; Cristian R. Calandra, MD; Pedro A. Kowacs, MD; John L. Berk, MD; Laura Obici, MD; Fabio A. Barroso, MD; MarkusWeiler, MD; Isabel Conceição, MD; ShiangtungW. Jung, PhD; Gustavo Buchele, PhD; Michela Brambatti, MD; Jersey Chen, MD, MPH; Steven G. Hughes, MBBS; Eugene Schneider, MD; Nicholas J. Viney, BSc; Ahmad Masri, MD; Morie R. Gertz, MD; Yukio Ando, MD; Julian D. Gillmore, PhD; Sami Khella, MD; P. James B. Dyck, MD; MárciaWaddington Cruz, PhD; for the NEURO-TTRansform Investigators

**Abstract**

**IMPORTANCE** Transthyretin gene silencing is an emerging treatment strategy for hereditary transthyretin (ATTRv) amyloidosis.

**OBJECTIVE** To evaluate eplontersen, an investigational ligand-conjugated antisense oligonucleotide, in ATTRv polyneuropathy.

**DESIGN, SETTING, AND PARTICIPANTS** NEURO-TTRansform was an open-label, single-group, phase 3 trial conducted at 40 sites across 15 countries (December 2019-April 2023) in 168 adults with Coutinho stage 1 or 2 ATTRv polyneuropathy, Neuropathy Impairment Score 10-130, and a documented TTR variant. Patients treated with placebo from NEURO-TTR (NCT01737398; March 2013–November 2017), an inotersen trial with similar eligibility criteria and end points, served as a historical placebo ("placebo") group.

**INTERVENTIONS** Subcutaneous eplontersen (45mg every 4 weeks; n = 144); a small reference group received subcutaneous inotersen (300mg weekly; n = 24); subcutaneous placebo weekly (in NEURO-TTR; n = 60).

**MAIN OUTCOMES AND MEASURES** Primary efficacy end points atweek 65/66were changes from baseline in serum transthyretin concentration, modified Neuropathy Impairment Score +7 (mNIS+7) composite score (scoring range, –22.3 to 346.3; higher scores indicate poorer function), and Norfolk Quality of Life Questionnaire–Diabetic Neuropathy (Norfolk QoL-DN) total score (scoring range, –4 to

136; higher scores indicate poorer quality of life). Analyses of efficacy end points were based on a mixed-effects model with repeated measures adjusted by propensity score weights.

**RESULTS** Among 144 eplontersen-treated patients (mean age, 53.0 years; 69%male), 136 (94.4%) completed week-66 follow-up; among 60 placebo patients (mean age, 59.5 years; 68%male), 52 (86.7%) completed week-66 follow-up. At week 65, adjusted mean percentage reduction in serum transthyretin was −81.7%with eplontersen and −11.2%with placebo (difference, −70.4%[95%CI, −75.2%to −65.7%]; P < .001). Adjusted mean change from baseline to week 66 was lower (better) with eplontersen vs placebo for mNIS+7 composite score (0.3 vs 25.1; difference, −24.8 [95%CI, −31.0 to −18.6; P < .001) and for Norfolk QoL-DN (−5.5 vs 14.2; difference, −19.7 [95%CI, −25.6 to −13.8]; P < .001). Adverse events by week 66 that led to study drug discontinuation occurred in 6 patients (4%) in the eplontersen group vs 2 (3%) in the placebo group. Through week 66, there were 2 deaths in the eplontersen group consistent with known disease-related sequelae (cardiac arrhythmia; intracerebral hemorrhage); there were no deaths in the placebo group. CONCLUSIONS AND RELEVANCE In patients with ATTRv polyneuropathy, the eplontersen treatment group demonstrated changes consistent with significantly lowered serum transthyretin concentration, less neuropathy impairment, and better quality of life compared with a historical placebo.

**Key Points**

**Question** Is the antisense oligonucleotide eplontersen associated with changes in serum transthyretin concentration and improvement in neuropathy symptoms among adults with hereditary transthyretin (ATTRv) amyloidosis with polyneuropathy?

**Findings** In this open-label study that enrolled 168 patients (144 assigned to subcutaneous eplontersen) and included 60 historical placebo patients, the eplontersen treatment group demonstrated changes from baseline to week 65/66 consistent with significantly lower serum transthyretin concentration (−81.7%vs −11.2%), less neuropathy impairment, and better quality of life compared with the historical placebo group.

**Meaning** Among adults with ATTRv polyneuropathy, the eplontersen treatment group had lower serum transthyretin concentration, less neuropathy impairment, and better quality of life compared with a historical placebo.

Hereditary transthyretin (ATTRv) amyloidosis is a life threatening autosomal dominant disease predominantly caused by single-point sequence variants in the TTR gene that codes for transthyretin, a thyroxine and vitamin A transporter.1-4 In ATTRv amyloidosis, abnormal transthyretin proteins misfold and aggregate into amyloid deposits in peripheral and autonomic nerves and other major organs (eg, heart, gastrointestinal tract, kidneys, eyes), resulting in progressive dysfunction with declines in quality of life (QoL).3,5,6 Death from complications of amyloid cardiomyopathy or cachexia typically occurs within 3 to 12 years after onset of symptoms, with cardiac involvement associated with particularly poor survival prognosis.2,7,8

Historically, disease-modifying treatment for ATTRv amyloidosis targeted hepatic production of circulating variant transthyretin through orthotopic liver transplantation,2,9 an invasive option with multiple challenges.4,10,11 The mechanism of earlier pharmacologic therapies (tafamidis, diflunisal) involved stabilizing the native transthyretin tetrameric structure.11-14 A more recent therapeutic strategy is TTR gene silencing by specifically targeting and degrading TTR messenger RNA in the liver. This approach has been clinically validated in phase 3 trials with subsequent regulatory approval of the small-interfering RNA therapies patisiran15 and vutrisiran,16 and the antisense oligonucleotide inotersen.17 Despite US Food and Drug Administration approval of several medications for ATTRv amyloidosis (tafamidis,18 inotersen,19 patisiran,20 and vutrisiran21), there remains a need for additional treatment options with even greater clinical benefits.

Eplontersen is an antisense oligonucleotide conjugated to a triantennary N-acetyl galactosamine (GalNAc) ligand for enhanced uptake by hepatocytes, the principal source of systemically circulating transthyretin protein. GalNAc conjugation increases the potency of antisense oligonucleotide molecules by 20- to 30-fold,22 allowing for use of substantially lower effective doses. In healthy volunteers,

subcutaneous eplontersen (45 mg every 4 weeks) (4 doses total) resulted in a mean 86% reduction from baseline in serum transthyretin concentration.23 The main objective of the phase 3 NEURO-TTRansform trial was to evaluate eplontersen in adults with ATTRv polyneuropathy compared with historical placebo, from the NEURO-TTR trial of inotersen.17

## Methods

### Study Design and Oversight

NEURO-TTRansform(NCT04136184)was a global, multicenter, open-label, phase 3 trial conducted from December 2019 through April 2023. The trial protocol and amendments (available in Supplement 1)were approved by the relevant local institutional review boards or ethics committees. The trial was conducted in adherence to the International Council for Harmonisation guidelines and relevant country-specific laws. Written informed consent was obtained from all patients prior to trial participation. An independent data and safety monitoring board regularly reviewed efficacy, safety, and tolerability data, including the results of a prespecified interim analysis at week 35.

The trial screened patients from45 sites in16countries and enrolled patients from 40 sites in 15 countries (Argentina, Australia, Brazil, Canada, Cyprus, France, Germany, Italy, New Zealand, Portugal, Spain, Sweden, Taiwan, Turkey, US). With concern that a prospective placebo-controlled study design would unnecessarily expose participants to sequelae from a rapidly progressive and potentially fatal neurologic disease, this trial was designed as a single-group trial with a historical placebo. The historical placebo group was derived from the week-66 end point of the randomized, double-blind, placebo-controlled, phase 3 inotersen trial in ATTRv polyneuropathy (NEURO-TTR [NCT01737398]), a study conducted between March 2013 and November 2017 that had similar eligibility criteria and end points as NEURO-TTRansform.17 In addition, a small inotersen reference group was included to allow for cross-trial

comparison of disease progression and treatment responses. Study design details24 and baseline patient characteristics25 have previously been published.

**Patients**

Adults aged 18 to 82 years with a diagnosis of Coutinho stage 1 (ambulatory without assistance) or 2 (ambulatory with assistance) ATTRv polyneuropathy were eligible for enrollment if they had a Neuropathy Impairment Score between 10 and 130 points (scores range from 0-244; higher scores indicate poorer function26) and a documented TTR sequence variant. Detailed inclusion and exclusion criteria have been published.24

Information regarding patient race and ethnicity was collected as consistent with the US Food and Drug Administration's ongoing efforts to address racial and ethnic demographics in clinical studies. Data on race and ethnicity were self-reported by the patients using a multiple-choice list.

**Randomization and Masking**

Patients were randomly assigned 6:1 with a blocking schema (block size of 7) to open-label treatment with eplontersen or inotersen (included as a small reference group; see Study Design and Oversight). Randomization was facilitated using an interactive voice/web-response system (IxRS; Almac).27

**Procedures**

Patients received subcutaneous eplontersen (45 mg every 4 weeks) until the final dose at week 81. In the inotersen reference group, subcutaneous inotersen (300 mg once every week) was administered up to and including the week-34 dose. Patients were then transitioned to eplontersen (45 mg every 4 weeks) from week 37 to week 81 (eFigure 1 in Supplement 2). Study treatment could be administered by study

center personnel or at home by the patient (or a caregiver/home health care provider). In NEURO-TTR, patients randomized to placebo received once-weekly subcutaneous placebo injections. All patients (eplontersen, inotersen, and historical placebo) were required to take oral supplementation of the recommended daily allowance of vitamin A (approximately 3000 IU daily).17,24

**Outcomes**

The final analysis end points were distributed over 2 visits (week 65 and week 66), as prespecified in the protocol. There were 3 primary efficacy end points, including percentage change from baseline in serum transthyretin concentration at week 65 and change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) composite score and Norfolk Quality of Life Questionnaire–Diabetic Neuropathy (Norfolk QoL-DN) total score, both at week 66. Serum transthyretin concentration was quantified using a custom-built electrochemiluminescence immunoassay on the Meso Scale Discovery platform at trough drug levels prior to study drug dosing. In NEURO-TTR, serum transthyretin concentration was measured using a validated commercial prealbumin assay using an immunoturbidometric method. To enable valid cross assay comparison, serum transthyretin concentrations from NEURO-TTR were adjusted to allow comparison to data generated using the electrochemiluminescence immunoassay. The mNIS+7 (scoring range, –22.3 to 346.3; higher scores indicate poorer function) is a modified version of the Neuropathy Impairment Score and was previously used in clinical trials of ATTRv polyneuropathy (eFigure 2 in Supplement 2).15-17 All mNIS+7 assessors were excluded from day-to-day care of the participants. All mNIS+7 scores were reviewed and normalized by a masked central reader at the Mayo Clinic's Peripheral Nerve Research Laboratory, who trained and certified the site-based assessors. The Norfolk QoL-DN Questionnaire is a neuropathy-specific tool that has been validated and used in clinical trials in patients with ATTRv polyneuropathy (scoring range, –4 to 136; higher scores indicate poorer QoL).13,15-17,28

Secondary efficacy end points, in hierarchical order, were changes from baseline in neuropathy symptom and change total score3 at weeks 35 and 66, 36-Item Short Form Survey physical component summary score29 at week 65, polyneuropathy disability (PND) score10 at week 65, and modified body mass index30 at week 65 (see Table 1 footnotes for scoring and interpretation of secondary end points).

Minimal clinically important differences are not established for the primary and secondary outcome scales for patients with ATTRv polyneuropathy.

Safety end points, as reported from baseline to week 66 for each patient, included treatment-emergent adverse events (TEAEs; coded using Medical Dictionary of Regulatory Activities version 25.0), serious TEAEs, and discontinuations due to TEAEs. Adverse events of special interest (AESIs) were identified as thrombocytopenia and glomerulonephritis, based on the safety profile of inotersen,17 as well as ocular events potentially related to vitamin A deficiency, which is a class-related precaution based on the role of transthyretin as a transporter of vitamin A–retinol binding complexes.19-21 It should be noted that serum vitamin A levels were available to NEURO-TTRansform investigators (eplontersen group) but were blinded per protocol in NEURO-TTR (historical placebo group) to avoid unmasking the double-blind treatment groups in the NEURO-TTR study. Injection site reactions, flulike symptoms, and TEAEs related to abnormal liver function were also summarized.

At week 85 (4 weeks after the last dose of study medication), exploratory end points included change from baseline in mNIS+7 composite score and Norfolk QoL-DN total score, and serum transthyretin concentration was assessed as a post hoc outcome.

**Sample Size Calculation**

Sample size estimations were predicated on attrition and outcome data fromNEURO-TTR.17 The planned sample of 140 patients (120 dosed with eplontersen), assuming a 10% rate of trial discontinuation, was estimated to have a power of at least 95% to detect a 70.3% difference (SD, 13%) in the percentage change from baseline in serum transthyretin concentration between eplontersen and historical placebo, a power of at least 90% to detect a 19.6-point difference (SD, 20) in change from baseline for themNIS+7composite score, and a power of at least 80% to detect a 10.7-point difference (SD, 20) in change from baseline for the Norfolk QoL-DN total score, using a 2-sided α of .025 for the assumed treatment effects and estimated SD.

**Statistical Analysis**

The efficacy analysis population included all patients who received at least 1 dose of trial medication (eplontersen or historical placebo) and who had a baseline and at least 1 post baseline mNIS+7 or Norfolk QoL-DN assessment. The safety analysis population included all patients who received at least 1 dose of trial medication (eplontersen or historical placebo).

Statistical analyses compared outcomes between the eplontersen and the historical placebo groups. The statistical analysis of percentage change from baseline in serum transthyretin concentration and change from baseline for all other primary and secondary efficacy end points was based on a mixed-effects model with repeated measures (MMRM) adjusted by propensity score weights (eAppendix 1 and eFigure 3 in Supplement 2). The MMRM contains fixed effects of treatment, time (categorical), disease stage,V30Mvariant, previous treatmentwith a transthyretin stabilizer, baseline value of the end point, treatment × time interaction, and the baseline × time interaction. Patients are random effects. Missing data were not imputed for MMRM analyses. The percentage change from baseline in serum transthyretin concentration was reported as mean, median, and interquartile range (25th-75th

percentiles). All end points were reported as least squares mean (hereafter, “adjusted mean”) and 95% CI for changes from baseline and as least-squares mean difference (hereafter, “difference”) and 95%CI for comparisons with historical placebo.

All primary and secondary end points were tested in hierarchical order of testing sequence using 2-sided tests with an overall type I error rate of 5%, as previously described (eFigure 4 in Supplement 2).24 The hierarchical testing procedure was based in part on the results of an interim efficacy analysis, which was conducted when all patients had completed week 35. The study was planned to proceed regardless of the results of the interim analysis, with further data collection performed for all study end points.

Efficacy analyses were performed in prespecified subgroups according to age, region, sex, V30M TTR sequence variant, previous treatment with stabilizers, disease stage, and diagnosis of cardiomyopathy. The subgroup analysis was based on the MMRM adjusted by propensity score weights. The model included fixed categorical effects for treatment, time, disease stage, V30M variant, and previous treatment; treatment × time interaction; treatment × subgroup interaction; and treatment × time × subgroup interaction. The baseline value of the end point and the baseline × time interaction were included as covariates in the model. There were 2 cardiomyopathy subgroups with different definitions. The cardiomyopathy baseline diagnosis–only subgroup was composed of patients with a clinical diagnosis of ATTRv cardiomyopathy on their case report form. The cardiomyopathy baseline diagnosis plus echocardiography subgroup was composed of patients with a clinical diagnosis of ATTRv cardiomyopathy on their case report form (ie, the cardiomyopathy baseline diagnosis–only subgroup) or interventricular septum thickness 13 mm or greater on baseline echocardiogram plus no hypertension (in past medical history or diagnosed during the trial) plus no 2 consecutive systolic blood pressure readings of 150 mm Hg or greater at any time during the trial (including screening and baseline visits).

As a post hoc analysis at week 66, individual components of the mNIS+7 and domains of the Norfolk QoL-DN were assessed based on the differences in adjusted means and corresponding 95% CIs. In another post hoc analysis, categorical descriptions of change from baseline in the mNIS+7 composite score and Norfolk QoL-DN total score were reported according to 10-point categories. The percentages of patients with improvement (score change from baseline <0) in mNIS+7 composite score and Norfolk QoL-DN total score were also calculated.

Safety data were compared descriptively between eplontersen and historical placebo. All statistical analyses were performed using SAS version 9.3 or later (SAS Institute Inc).

**Results**

**Patient Characteristics**

Between December 2019 and June 2021, a total of 217 patients were screened. Of these, 144 patients were randomized to receive eplontersen and 24 patients were randomized to the inotersen reference group (Figure 1). The safety analysis population included all 144 patients in the eplontersen group and 60 patients from the historical placebo (hereafter, “placebo”) group. The efficacy analysis population comprised 141 patients in the eplontersen group and 59 patients from the placebo group (3 patients in the eplontersen group and 1 in the placebo group did not have any post baseline mNIS+7 or Norfolk QoL-DN assessments). In the eplontersen group, 136 of 144 patients (94.4%) completed week 66; in the placebo group, 52 of 60 (86.7%) completed NEUROTTR week 66. The eplontersen and placebo groups were generally well balanced across baseline characteristics (Table 1). Patients in the eplontersen group were slightly younger, had less severe disease, were more likely to have received previous treatment with stabilizers, and were more likely to have the V30M variant (associated primarily with

polyneuropathy10) than those in the placebo group. TTR sequence variants noted in 10% or more of patients were V30M (59%) and A97S (15%) in the eplontersen group and V30M (55%) and T60A (13%) in the placebo group (eTable 1 in Supplement 2). The V122I variant, which is associated with a predominantly cardiomyopathy phenotype,32 was reported for 3% and 2% of patients in the eplontersen and placebo groups, respectively.

Baseline demographics and characteristics of the inotersen reference group and the inotersen group from NEURO-TTR are provided in eTable 2 in Supplement 2 for reference. Efficacy outcomes for the 2 inotersen groups at week 35 are presented in eTable 3 in Supplement 2.Change in serum transthyretin concentration in the inotersen reference group (eFigure 5 in Supplement 2) shows a qualitatively similar trajectory of steep initial decline followed by leveling off of the slope as was seen in the inotersen group in NEURO-TTR.17

**Interim Analysis**

The interim analysis at week 35 demonstrated an adjusted mean percentage reduction in serum transthyretin concentration of −81.2% in the eplontersen group and −14.8%in the placebo group (difference, −66.4%[95%CI, −71.4%to −61.5%]; P < .001) (eTable 4 in Supplement 2). The adjusted mean change from baseline to week 35 in mNIS+7 composite score was 0.2 in the eplontersen group and 9.2 in the placebo group (difference, −9.0 [95% CI, −13.5 to −4.5]; P < .001). The adjusted mean change from baseline to week 35 in Norfolk QoL-DN total score was –3.1 in the eplontersen group and 8.7 in the placebo group (difference, −11.8 [95%CI, −16.8 to −6.8]; P < .001).

**Primary Outcomes**

At week 65, the adjusted mean percentage reduction in serum transthyretin was −81.7%in the eplontersen group and −11.2% in the placebo (difference, −70.4%[95%CI, −75.2%to −65.7%]; P < .001) (Figure 2A shows the mean percentage reduction).

The adjusted mean change from baseline to week 66 in mNIS+7 composite score was0.3 in the eplontersen group and 25.1 in the placebo group (difference, −24.8 [95%CI, −31.0 to −18.6]; P < .001). The adjusted mean change from baseline to week 66 in Norfolk QoL-DN total score was –5.5 in the eplontersen group and 14.2 in the placebo group (difference, −19.7 [95% CI, −25.6 to −13.8]; P < .001) (Figure 2B and Figure 2C).

Parallel line plots of change from baseline for TTR and change from baseline formNIS+7 and Norfolk QoL-DN, the primary efficacy end points, are provided in eFigure 6 in Supplement 2. For all primary efficacy end points, consistent treatment effect was also demonstrated across prespecified subgroups at week 66 (eFigure 7 in Supplement 2).

**Secondary Outcomes**

Across all secondary efficacy end points, differences between eplontersen and placebo were statistically significant. Adjusted mean change from baseline to week 35 in neuropathy symptom and change total score was 0.8 in the eplontersen group and 4.7 in the placebo group (difference, −3.9 [95% CI, −6.1 to −1.8]; P < .001]); at week 66, the changes from baseline were –0.03 and 8.2 in the eplontersen and placebo groups, respectively (difference, −8.2 [95% CI, −10.7 to −5.8]; P < .001) (Figure 3A). Adjusted mean change from baseline to week 65 in 36-Item Short Form Survey physical component summary score was 0.9 with eplontersen and –4.5 with placebo (difference, 5.3 [95% CI, 3.2-7.4]; P < .001) (Figure 3B). In the eplontersen group, the proportion of patients with PND score I was unchanged from baseline

at week 65 (39.6% at both time points) (Figure 3C); in the placebo group, the proportion of patients with PND score I decreased from 37.3% at baseline to 29.4% at week 65. Compared with the eplontersen group, the placebo group had a larger proportion of patients with PND score IIIa at baseline (25.5% vs 10.4%); in both groups, the proportion of patients with PND score IIIa increased approximately 2% from baseline to week 65. The proportion of patients with PND score IIIb decreased slightly in the eplontersen group from 6.7% to 6.0% but increased in the placebo group from 5.9% to 11.8%. In both groups, the proportion of patients with PND score IV went from 0% at baseline to 2% at week 65. The adjusted mean change from baseline to week 65 in modified body mass index, a measure of nutritional status, was –8.1 kg/m2 × g/L in the eplontersen group and –90.8 kg/m2 × g/L in the historical placebo group (difference, 82.7 kg/m2 × g/L [95% CI, 54.6-110.8]; P < .001) (Figure 3D).

**Exploratory and Post Hoc Analyses**

The changes in mNIS+7 composite score and Norfolk QoL-DN total score were consistent across the individual components of the mNIS+7 and domains of the Norfolk QoL-DN questionnaire (eFigure 8 in Supplement 2).

Overall, 47% and 58% of patients treated with eplontersen had score reductions from baseline toweek66inmNIS+7 composite score and Norfolk QoL-DN total score, respectively (lower scores represent better function/QoL); in the placebo group, 17% and 20% had score reductions at week 66 (eFigure 9 in Supplement 2). Among study completers, 53% and 65%of patients treated with eplontersen had score reductions from baseline in mNIS+7 composite score and Norfolk QoL-DN total score, respectively; 19% and 23% of placebo patients had score reductions in these outcomes, respectively, at week 66. These data are also shown graphically for individual patients in eFigure 6 in Supplement 2.

Changes from baseline to week 85 in serum transthyretin concentration, mNIS+7 composite score, and NorfolkQoL-DN total score can be found in eFigure 10 and eTable 6 in Supplement 2.Changes from baseline toweek85 in neuropathy symptom and change total score and 36-Item Short Form Survey physical component summary are shown in eFigure 11 in Supplement 2.

**Adverse Events**

For the eplontersen vs placebo groups, respectively, overall frequencies of TEAEs were 97% vs 100%, and serious TEAEs occurred in 15% vs 20% (Table 2). For 74 of 144 patients (51%) in the eplontersen group, TEAEs were rated as mild. The most frequently reported TEAEs in the eplontersen group were COVID-19, diarrhea, urinary tract infection, vitamin A deficiency, and nausea (eTable 5 in Supplement 2). Two deaths were reported in the eplontersen group by week 66 (arrhythmia and cerebral hemorrhage in setting of normal platelet count); 1 death was reported between week 66 and week 85 (acute myocardial infartion). All deaths were potentially related to ATTRv amyloidosis33; none were considered drug-related. Overall, treatment was discontinued due to a TEAE in 6 patients (4%) in the eplontersen group and 2 patients (3%) in the placebo group.

Within the AESIs, thrombocytopenia was reported in 3 patients (2%) in the eplontersen group (4 events) and 1 (2%) in the placebo group (2 events). All thrombocytopenia events in the eplontersen group were rated as mild, did not lead to any bleeding events, and were recovered from with no dosing change or interruption and without sequelae. Nadir platelet counts in these 3 patients in the eplontersen group with an AESI of thrombocytopenia were between 102 × 109/L and 136 × 109/L. Therewere 2 cases of potential glomerulonephritis reported, both in the placebo group. The proportions of patients with the AESI of ocular events potentially related to vitamin A deficiency were similar between eplontersen and placebo (17%vs 15%).No patient experienced ocular TEAEs assessed by ophthalmic examination to be

consistent with vitamin A deficiency. Injection site reactions occurred in 8%of patients in the eplontersen group and 12% in the placebo group. Flu-like symptoms were reported in zero patients in the eplontersen group and 2 (3%) in the placebo group. TEAEs related to abnormal liver function were reported in 9 patients (6%) in the eplontersen group and 4 (7%) in the historical placebo group. There were no Hy law (severe drug-induced liver injury31) cases.

No patient in either group discontinued study drug due to an AESI or COVID-19 (eAppendix 2 in Supplement 2).

**Discussion**

Patients with ATTRv polyneuropathy treated with eplontersen, as compared with historical placebo, demonstrated study outcomes associated with significantly lowered serum transthyretin concentration, less neuropathy impairment, and better QoL. Where assessed, the study outcome differences between the eplontersen and historical placebo groups were independent of a range of baseline patient characteristics and were consistent across individual components of multicomponent outcome measures.

Treatment-emergent adverse events reported in patients treated with eplontersen were consistent with an integrated class safety analysis of data from 7 phase 2 studies for 6 GalNAc-conjugated antisense oligonucleotides (pooled n = 512 patients).34 The TEAEs were mild in 51% of patients, and the incidence of treatment discontinuation due to TEAEs was low. The incidence of AESIs of thrombocytopenia was similar in the eplontersen and historical placebo groups; the few cases that occurred in the eplontersen group were mild and resolved without dosing interruption. In NEURO-TTR, 15 patients (13%) receiving inotersen reported a TEAE of thrombocytopenia. Three (3%) of these cases were grade 4; of these, 2

necessitated discontinuation of inotersen and treatment with glucocorticoids, and 1 was associated with a fatal intracranial hemorrhage.17 There were no cases of glomerulonephritis in the eplontersen group in NEURO-TTRansform, while 3% of patients receiving inotersen in NEURO-TTR developed serious glomerulonephritis that was considered related to treatment.17 Reduced risk of AESIs was a hypothesized benefit of the GalNAc-conjugated structure of eplontersen, which allows for lower dose exposure relative to inotersen (45 mg every 4 weeks vs 300 mg every week).

The rates of ocular events were similar between the eplontersen group and historical placebo group (17% vs 15%), even though the eplontersen group had a greater incidence of vitamin A deficiency/decreased/abnormal TEAE. The 2 deaths reported through week 66 were consistent with known amyloidosis sequelae (intracerebral hemorrhage, cardiac arrhythmia),33 and the mortality rate (2/144 eplontersen exposed patients [1%]) was comparable to that reported for active treatment, and comparable to or lower than that reported for placebo, in other randomized, placebo controlled clinical trials in similar populations with ATTRv polyneuropathy.11,15-17 Longer-term safety and tolerability of eplontersen are being assessed in an ongoing open-label extension study, which will provide further data.

This study adds to the growing body of evidence related to TTR gene silencing in general, and hepatic-targeted therapies in particular, for patients with ATTRv polyneuropathy,15-17,35and these therapies are suggested as among first-line treatments in ATTRv amyloidosis expert consensus statements.4

**Limitations**

This study has several limitations. First, the analysis included a single-group, prospective, active treatment group and a historical placebo group from a study conducted several years prior. A concurrent

placebo group was considered unethical in a study involving individuals with a rapidly progressive and potentially fatal neurologic disease for which effective treatment options are available. As compared with a double blind, randomized study, the historical placebo design has some potential limitations with respect to potential bias, because the population and natural history of disease from 2 studies performed at different times may vary. However, given the magnitude of the observed treatment effect, it is unlikely that any potentially introduced biases would have affected the overall conclusion that eplontersen met its primary and secondary end points.

Second, there were a few minor differences in baseline characteristics between the eplontersen and historical placebo groups. For example, the historical placebo group was older, with a higher proportion of patients with advanced disease and associated cardiomyopathy, differences that may, in part, reflect changing epidemiologic patterns of diagnosed patients over recent years. The use of propensity score–adjusted analyses was implemented in an effort to limit potential bias due to different baseline characteristics between groups.

Third, although the study included an inotersen reference group as a cross-study comparison, only a small number of patients were included in this group and the comparability of the 2 inotersen groups (NEURO-TTRansform vs NEUROTTR) could only be qualitatively assessed.

Fourth, the trial excluded patients with the most severe disease (Coutinho stage 3), which may limit applicability of the findings for such patients.

Fifth, as is true for many clinical trials, especially in rare diseases, the study was not powered to assess differences in TEAEs between the treatment groups. Longer-term assessment of safety findings from an open-label extension to NEURO-TTRansform will be reported in the future.

## Conclusions

In patients with ATTRv polyneuropathy, the eplontersen treatment group demonstrated changes consistent with significantly lowered serum transthyretin concentration, less neuropathy impairment, and better quality of life compared with a historical placebo.

**Author Affiliations**

Centro Hospitalar Universitário de Santo António, Porto, Portugal (Coelho); Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto, Brazil (Marques); Indiana University School of Medicine, Indianapolis (Dasgupta); National Taiwan University Hospital, Taipei, Taiwan (Chao); İstanbul Üniversitesi–Istanbul Tıp Fakültesi, Istanbul, Turkey (Parman); Universidade Estadual de Campinas, Campinas, São Paulo, Brazil (França); China Medical University Hospital, Taichung, Taiwan (Guo); Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden (Wixner); Chang Gung Memorial Hospital, Linkou Medical Center, Taoyuan, Taiwan (Ro); Hospital El Cruce, Buenos Aires, Argentina (Calandra); Instituto de Neurologia de Curitiba, Curitiba, Paraná, Brazil (Kowacs); Boston University School of Medicine, Boston, Massachusetts (Berk); Amyloidosis Research and Treatment Centre, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy (Obici); Neurology Department, Fleni, Buenos Aires, Argentina (Barroso); Amyloidosis Center and Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany (Weiler); Centro Hospitalar Universitário Lisboa-Norte, Hospital de Santa Maria, Lisbon, Portugal (Conceição); Ionis Pharmaceuticals Inc, Carlsbad, California (Jung, Buchele, Brambatti, Hughes, Schneider, Viney); Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, Maryland (Chen); OHSU Center for Hypertrophic Cardiomyopathy and Amyloidosis, Portland, Oregon (Masri); Mayo Clinic, Rochester, Minnesota (Gertz, Dyck); Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan (Ando); National Amyloidosis Centre, University College London, London, United Kingdom (Gillmore); University of Pennsylvania School of Medicine, Philadelphia (Khella); Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil (Waddington Cruz).

**Author Contributions**

Drs Coelho and Waddington-Cruz had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Coelho, Dasgupta, Conceição, Jung, Buchele, Brambatti, Schneider, Viney, Ando.

*Acquisition, analysis, or interpretation of data*: Coelho, Marques Jr, Chao, Parman, França Jr, Guo, Wixner, Ro, Calandra, Kowacs, Berk, Obici, Barroso, Weiler, Jung, Buchele, Brambatti, Chen, Hughes, Schneider, Viney, Masri, Gertz, Gillmore, Khella, Dyck, Waddington Cruz.

*Drafting of the manuscript*: Marques Jr, Dasgupta, Ro, Calandra, Berk, Jung, Brambatti, Chen, Schneider, Viney, Ando, Khella.

*Critical review of the manuscript for important intellectual content*: Coelho, Marques Jr, Chao, Parman, França Jr, Guo, Wixner, Ro, Kowacs, Berk, Obici, Barroso,Weiler, Conceição, Buchele, Hughes, Schneider, Viney, Masri, Gertz, Gillmore, Dyck, Waddington Cruz.

*Statistical analysis:* Jung.

*Administrative, technical, or material support:* Marques Jr, França Jr, Guo, Wixner, Ro,Weiler, Hughes, Gertz.

*Supervision:* Coelho, Dasgupta, Chao, França Jr, Calandra, Obici,Weiler, Conceição, Buchele, Brambatti, Chen, Schneider, Viney, Masri, Ando, Khella.

**Conflict of Interest Disclosures**

Dr Coelho reported receiving consulting fees (to institution) from Ionis and AstraZeneca and receiving support for scientific meetings attendance from Sobi, Pfizer, and Alnylam. Dr Marques Jr reported receiving personal fees for participation in meetings, lectures, and advisory boards from Alnylam, PTC Therapeutics, and Pfizer. Dr Dasgupta reported receiving personal fees for serving on the advisory board of NorvoNordisk, Eidos, Alnylam, AstraZeneca, and Intellia/Regeneron; receiving nonfinancial writing

assistance from Eidos; receiving nonfinancial travel support from the American Society of Hematology; and receiving grants from Ionis. Dr França Jr reported receiving personal fees for participation in in meetings, lectures, and advisory boards from Alnylam, PTC Therapeutics, and Pfizer and receiving research grants from Pfizer and PTC. Dr Wixner reported receiving consulting fees from Akcea Therapeutics, AstraZeneca, Alnylam Pharmaceuticals, Pfizer, and Intellia Therapeutics. Dr Calandra reported receiving clinical research honoraria from Ionis Pharmaceuticals. Dr Kowacs reported receiving for regular research activities from Ionis. Dr Berk reported receiving study funding from Alnylam Pharmaceuticals, Ionis/AstraZeneca, and Eidos/BridgeBio; receiving consulting fees from Alnylam Pharmacauticals, Ionis/AstraZeneca, Intellia Therapeutics, and AO Pharma; serving on ad hoc advisory boards for Ionis/AstraZeneca, Eidos/BridgeBio, Intellia Therapeutics; and serving on the advisory board for Corino Therapeutics. Dr Obici reported receiving consulting fees from Pfizer, Alnylam, Sobi, Novo Nordisk, BridgeBio, and AstraZeneca and receiving speaker fees from Pfizer, Alnylam, and Sobi. Dr Barroso reported receiving personal fees from Ionis Pharmaceuticals. Dr Weiler reported receiving consulting fees from Akcea Therapeutics, Alnylam Pharmaceuticals, Biogen, Hoffmann-La Roche, Novo Nordisk, Pfizer, and Sobi; receiving speaker fees from Akcea Therapeutics, Alnylam Pharmaceuticals, and Biogen; and receiving financial support for conference attendance from Akcea Therapeutics, Alnylam Pharmaceuticals, Ionis Pharmaceuticals, and Pfizer. Dr Conceição reported receiving personal fees from Alnylam Pharmaceuticals and Akcea and receiving grants from Pfizer. Dr Buchele reported being a former employee of Ionis Pharmaceuticals. Dr Chen reported holding stock shares in AstraZeneca. Dr Hughes reported serving as a paid consultant to Ionis Pharmaceuticals. Dr Masri reported receiving grants from Pfizer, Ionis, Cytokinetics, and Ultromics and receiving personal fees from Cytokinetics, Bristol Myers Squibb, Eidos, Pfizer, Ionis, Alnylam, Attralus, Haya, BioMarin, Lexicon, and Tenaya. Dr Gertz reported receiving personal fees from Ionis, Alnylum, Prothena, Janssen, Sanofi, Juno, Physicians Education Resource, Johnson & Johnson, Celgene, and Research to Practice; serving on the data and safety

monitoring board for Abbvie; receiving grants from Aptitude Health; receiving meeting fees from Ashfield and Sorrento; and developing educational materials for i3Health. Dr Gillmore reported receiving consulting fees from Alnylam, Intellia, AstraZeneca, ATTRalus, Ionis, BridgeBio, and Pfizer. Dr Khella reported receiving consulting fees from Ionis and Alnylum. DrWaddington Cruz reported receiving personal fees from Ionis for acting as principal investigator in the current trial and receivinf consulting fees from Alnylam, Pfizer, and AstraZeneca. No other disclosures were reported.

**Funding/Support:** This study was sponsored by Ionis Pharmaceuticals Inc.

**Role of the Funder/Sponsor:** Ionis Pharmaceuticals Inc was involved in design and conduct of the study; management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Group Information:** The NEURO-TTRansform Investigators appear in Supplement 3.

**Previous Presentation:** This work was presented in part in an oral presentation at the Peripheral Nerve Society Annual Meeting; Copenhagen, Denmark; June 17-20 2023; and in an oral presentation and poster at the American Academy of Neurology Annual Meeting; Boston, Massachusetts; April 22-27, 2023.

**Data Sharing Statement:** See Supplement 4.

**Additional Contributions:** We thank the study participants and caregivers, the NEURO-TTRansform Study Investigators, Ionis Pharmaceuticals Inc, and AstraZeneca for their participation and/or contribution. Medical writing and editorial assistance were provided by Sandra Westra, PharmD, and Jessica D. Herr, PharmD, of Peloton Advantage LLC, an OPEN Health company, and funded by Ionis Pharmaceuticals Inc.

References

1. Skrahina V, Grittner U, Beetz C, et al. Hereditary transthyretin-related amyloidosis is frequent in polyneuropathy and cardiomyopathy of no obvious aetiology. *Ann Med*. 2021;53(1):1787-1796. doi:10.1080/07853890.2021.1988696

2. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol*. 2021;268(6):2109-2122. doi:10.1007/s00415-019-09688-0

3. Dyck PJB, Coelho T,Waddington Cruz M, et al. Neuropathy symptom and change: inotersen treatment of hereditary transthyretin amyloidosis. *Muscle Nerve*. 2020;62(4):509-515. doi:10.1002/mus.27023

4. Ando Y, Adams D, Benson MD, et al. Guidelines and new directions in the therapy and monitoring of ATTRv amyloidosis. *Amyloid*. 2022;29(3):143-155. doi:10.1080/13506129.2022.2052838

5. Schmidt HH,Waddington-Cruz M, Botteman MF, et al. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. *Muscle Nerve*. 2018;57(5):829-837. doi:10.1002/mus.26034

6. Conceição I, González-Duarte A, Obici L, et al. “Red-flag” symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2016;21(1):5-9. doi:10.1111/jns.12153

7. Planté-Bordeneuve V, Kerschen P. Transthyretin familial amyloid polyneuropathy. *Handb Clin Neurol*. 2013;115:643-658. doi:10.1016/B978-0-444-52902-2.00038-2

8. Jang SC, Nam JH, Lee SA, et al. Clinical manifestation, economic burden, and mortality in patients with transthyretin cardiac amyloidosis. *Orphanet J Rare Dis*. 2022;17(1):262. doi:10.1186/s13023-022-02425-3

9. Ericzon BG, Wilczek HE, Larsson M, et al. Liver transplantation for hereditary transthyretin amyloidosis: after 20 years still the best therapeutic alternative? *Transplantation*. 2015;99(9):1847-1854. doi:10.1097/TP.0000000000000574

10. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis*. 2013;8:31. doi:10.1186/1750-1172-8-31

11. Berk JL, Suhr OB, Obici L, et al; Diflunisal Trial Consortium. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA*. 2013;310(24):2658-2667. doi:10.1001/jama.2013.283815

12. Sekijima Y, Dendle MA, Kelly JW. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. *Amyloid*. 2006;13(4):236-249. doi:10.1080/13506120600960882

13. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology*. 2012;79(8):785-792. doi:10.1212/WNL.0b013e3182661eb1

14. Barroso FA, Judge DP, Ebede B, et al. Long-term safety and efficacy of tafamidis for the treatment of hereditary transthyretin amyloid polyneuropathy: results up to 6 years. *Amyloid*. 2017;24(3):194-204. doi:10.1080/13506129.2017.1357545

15. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379 (1):11-21. doi:10.1056/NEJMoa1716153

16. Adams D, Tournev IL, Taylor MS, et al; HELIOS-A Collaborators. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):1-9. doi:10.1080/13506129.2022.2091985

17. Benson MD,Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379 (1):22-31. doi:10.1056/NEJMoa1716793

18. Vyndaqel and Vyndamax [package insert]. Pfizer Inc; 2021.

19. Tegsedi [package insert]. Akcea Therapeutics Inc; 2022.

20. Onpattro [package insert]. Alnylam Pharmaceuticals Inc; 2021.

21. Amvuttra [package insert]. Alnylam Pharmaceuticals Inc; 2022.

22. Wang Y, Yu RZ, Henry S, Geary RS. Pharmacokinetics and clinical pharmacology considerations of GalNAc3-conjugated antisense oligonucleotides. *Expert Opin Drug Metab Toxicol*. 2019;15(6):475-485. doi:10.1080/17425255.2019. 1621838

23. Viney NJ, Guo S, Tai LJ, et al. Ligand conjugated antisense oligonucleotide for the treatment of transthyretin amyloidosis: preclinical and phase 1 data. *ESC Heart Fail*. 2021;8(1):652-661. doi:10.1002/ehf2.13154

24. Coelho T, Ando Y, Benson MD, et al. Design and rationale of the global phase 3 NEURO-TTRansform study of antisense oligonucleotide AKCEA-TTR-LRx (ION-682884-CS3) in hereditary transthyretin mediated amyloid polyneuropathy. *Neurol Ther*. 2021;10(1):375-389. doi:10.1007/s40120-021-00235-6

25. Coelho T,Waddington Cruz M, Chao CC, et al. Characteristics of patients with hereditary transthyretin amyloidosis–polyneuropathy (ATTRv-PN) in NEURO-TTRansform, an open-label phase 3 study of eplontersen. *Neurol Ther*. 2023;12 (1):267-287. doi:10.1007/s40120-022-00414-z

26. Dyck PJB, González-Duarte A, Obici L, et al. Development of measures of polyneuropathy impairment in hATTR amyloidosis: from NIS to mNIS + 7. *J Neurol Sci*. 2019;405:116424. doi:10. 1016/j.jns.2019.116424

27. Ruikar V. Interactive voice/web response system in clinical research. *Perspect Clin Res*. 2016;7(1):15-20. doi:10.4103/2229-3485.173781

28. Vinik EJ, Vinik AI, Paulson JF, et al. Norfolk QOL-DN: validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. 2014;19(2):104-114. doi:10.1111/jns5.12059

29. McHorney CA,Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36), III: tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care*. 1994;32(1):40-66. doi:10.1097/00005650-199401000-00004

30. Suhr O, Danielsson A, Holmgren G, Steen L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *J Intern Med*. 1994;235(5):479-485. doi:10.1111/j.1365-2796.1994.tb01106.x

31. Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. US Food and Drug Administration. Published July 2009. Accessed July 7, 2023. https://www.fda.gov/media/116737/download

32. Rapezzi C, Quarta CC, Obici L, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. *Eur Heart J*. 2013;34(7):520-528. doi:10.1093/eurheartj/ehs123

33. Sekijima Y. Hereditary transthyretin amyloidosis. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews*. University of Washington; 1993.

34. Baker BF, Xia S, PartridgeW, et al. Integrated assessment of phase 2 data on GalNAc3-conjugated 2'-O-methoxyethyl-modified antisense oligonucleotides. *Nucleic Acid Ther*. 2023;33(1):72-80. doi:10.1089/nat.2022.0044

35. Brannagan TH III, Berk JL, Gillmore JD, et al. Liver-directed drugs for transthyretin-mediated amyloidosis. *J Peripher Nerv Syst*. 2022;27(4):228-237. doi:10.1111/jns.12519

**Tables**

**Table 1.** Patient Demographics and Baseline Clinical Characteristics[a]

| Characteristic | Eplontersen (n=144) | Historical placebo (n = 60) |
|---|---|---|
| Age, mean (SD), y | 53.0 (15.0) | 59.5 (14.0) |
| Sex, No. (%)[b] | | |
| Female | 44 (31) | 19 (32) |
| Male | 100 (69)) | 41 (68 |
| Race, No. (%)[c] | n = 143 | |
| Asian | 22 (15) | 3 (5) |
| Black or African American | 5 (3) | 1 (2) |
| White | 112 (78) | 53 (88) |
| Other or multiple | 4 (3) | 3 (5) |
| Geographic region, No. (%) | | |
| North America | 21 (15) | 26 (43) |
| Europe | 54 (38) | 23 (38) |
| South America/Australia/Asia | 69 (48) | 11 (18) |
| Body weight, kg | n = 141 | |
| Mean (SD) | 70.3 (15.8) | 71.1 (18.1) |
| BMI | n = 138 | |
| Mean (SD) | 24.4 (4.9) | 24.2 (4.9) |
| Modified BMI, $kg/m^2 \times g/L$[d]) | n = 138 | |
| Mean (SD) | 1025.8 (235.1) | 1049.9 (228.4 |

| | | |
|---|---|---|
| Albumin, g/L, mean (SD) | 42.2 (2.9) | 43.5 (3.1) |
| TTR variant, No. (%) | | |
| V30M | 85 (59) | 33 (55) |
| Non-V30Me | 59 (41) | 27 (45) |
| Coutinho stage, No. (%) | | |
| 1 (ambulatory without assistance) | 115 (80) | 42 (70) |
| 2 (ambulatory with assistance) | 29 (20) | 18 (30) |
| Polyneuropathy disability score, No. (%)[f] | n = 143 | |
| I (sensory disturbances but preserved walking capability) | 56 (39) | 23 (38) |
| II (impaired walking capability but ability to walk without a stick or crutches) | 61 (43) | 19 (32) |
| IIIa (walking only with the help of 1 stick or crutch) | 16 (11) | 15 (25) |
| IIIb (walking with the help of 2 sticks or crutches) | 10 (7) | 3 (5) |
| IV (confined to a wheelchair or bedridden) | 0 | 0 |
| Previous treatment with tafamidis or diflunisal, No. (%) | 100 (69) | 36 (60) |
| Duration of disease from diagnosis of ATTRv polyneuropathy, median (IQR),mo[g] | 30.0 (8.0 to 59.5) | 24.0 (7.0 to 64.0) |

| | | |
|---|---|---|
| Duration of disease from onset of symptoms of ATTRv polyneuropathy (n = 143 for eplontersen), median (IQR),mo[g] | 54.0 (31.0 to 93.0) | 48.0 (28.0 to 88.5) |
| ATTRv cardiomyopathy clinical diagnosis from CRF | | |
| Cardiomyopathy baseline diagnosis-only subgroup, No. (%) | 39 (27) | 22 (37) |
| Cardiomyopathy baseline diagnosis + echocardiography subgroup, No. (%)[h] | 49 (34) | 30 (50) |
| mNIS+7 composite score, mean (SD)[i] | 81.3 (43.4) | 74.8 (39.0) |
| Norfolk QoL-DN total score | n = 137 | n = 59 |
| Mean (SD)[j] | 44.1 (26.6) | 48.7 (26.7) |
| NSC total score, mean (SD)[k] | 23.1 (12.4) | 23.0 (12.6) |
| SF-36 PCS score, mean (SD)[l] | 39.7 (9.3) | 37.2 (9.8) |

Abbreviations: ATTRv, hereditary transthyretin; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); CRF, case report form; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QoL-DN, Norfolk Quality of Life Questionnaire–Diabetic Neuropathy; NSC, neuropathy symptom and change; SF-36 PCS, 36-Item Short Form Survey physical component summary.

[a]Percentages may not total 100 due to rounding.

[b]Observed or classified by the investigator.

[c]Self-reported by patients using a multiple-choice list or free text for "Other." Information regarding race was collected as consistent with US Food and Drug Administration ongoing efforts to address racial demographics in clinical studies.31

[d]Defined as body mass index in kg/m2 × albumin level in g/L; higher scores indicate better nutritional status.30

[e]A breakdown of non-V30M variant distribution is provided in eTable 1 in Supplement 2.

[f]Scores range from I to IV, with higher scores indicating worse disability.10

[g]Time from diagnosis or onset of symptoms (collected as year and month only) to date of informed consent.

[h]Patients with (1) a clinical diagnosis of ATTRv cardiomyopathy on their case report form (ie, cardiomyopathy baseline diagnosis-only subgroup) or (2) interventricular septum thickness 13mmor greater on baseline echocardiogram plus no hypertension (in past medical history or diagnosed during the trial) plus no 2 consecutive systolic blood pressure readings of 150mmHg or greater at any time during the trial (including screening and baseline visits).

[i]Scores range from −22.3 to 346.3; higher scores indicate poorer function.26

[j]Total scores on the Norfolk QoL-DN questionnaire range from −4 to 136, with higher scores indicating poorer quality of life.17

[k]NSC Scores range from 0 to 114 (men) or 108 (women); higher scores indicate worse symptoms.3

[l]Scores range from 0 to 100; higher scores indicate better physical health–related quality of life.29

**Table 2**. Summary of Treatment-Emergent Adverse Events[a]

| | No. (%) | |
|---|---|---|
| | Eplontersen (n = 144) | Historical placebo (n = 60) |
| Any TEAE | 140 (97) | 60 (100) |
| Leading to study drug discontinuation[b] | 6 (4) | 2 (3) |
| Maximum severity of TEAEs | | |
| Mild | 74 (51) | 7 (12) |
| Moderate | 53 (37) | 40 (67) |
| Severe | 13 (9) | 13 (22) |
| Adverse events of special interest[c] | 41 (29) | 12 (20) |
| Vitamin A deficiency/decreased/abnormal[d] | 23 (16) | NR[e] |
| Ocular events potentially related to vitamin A deficiency[f] | 24 (17) | 9 (15) |
| Thrombocytopenia | 3 (2) | 1 (2) |
| Glomerulonephritis | 0 | 2 (3)[g] |
| Leading to study drug discontinuation | 0 | 0 |
| Injection site reactions | 12 (8) | 7 (12) |
| Flu-like symptoms[i] | 0 | 2 (3) |
| Abnormal liver function[j] | 9 (6) | 4 (7) |
| Any serious TEAE | 21 (15) | 12 (20) |
| Related to study drug | 0 | 1 (2) |
| Death | 2 (1)[k] | 0 |
| Death due to study drug | 0 | 0 |

Abbreviations: NR, not reportable; TEAE, treatment-emergent adverse event.

[a]Defined as adverse events that first occurred, or worsened, after first dose of study drug at week-66 analysis. TEAE data through week 85 are reported in eTables 8 and 9 in Supplement 2.

[b]Historical placebo group: 1 pain at administration site, weight increase, arthralgia; 1 proteinuria (stopping rule met). Eplontersen group: 1 fatal cardiac arrhythmia, 1 fatal intracerebral hemorrhage, 1 urosepsis, 1 proteinuria, 1 kidney impairment, 1 abnormal transaminase levels (the TEAE started before week 66 and patient's last dose was before week 66, but patient discontinued study drug after week 66).

[c]Definitions provided in eTable 10 in Supplement 2.

[d]Serum vitamin A levels were available to NEURO-TTRansform investigators (eplontersen group) but were blinded per protocol in NEURO-TTR (placebo group) to avoid unmasking the double-blind treatment groups.

[e]In NEURO-TTR, vitamin A levels were blinded from investigators during the study, so event was not reportable as a TEAE.

[f]An ocular questionnaire to screen for vitamin A deficiency was administered periodically (every 2-3 months) during the treatment period in NEURO-TTRansform; assessments were not used in NEURO-TTR. In cases of suspected vitamin A deficiency, an ophthalmologist consultation could have been requested by the investigator, if necessary, after discussing with the medical monitor.

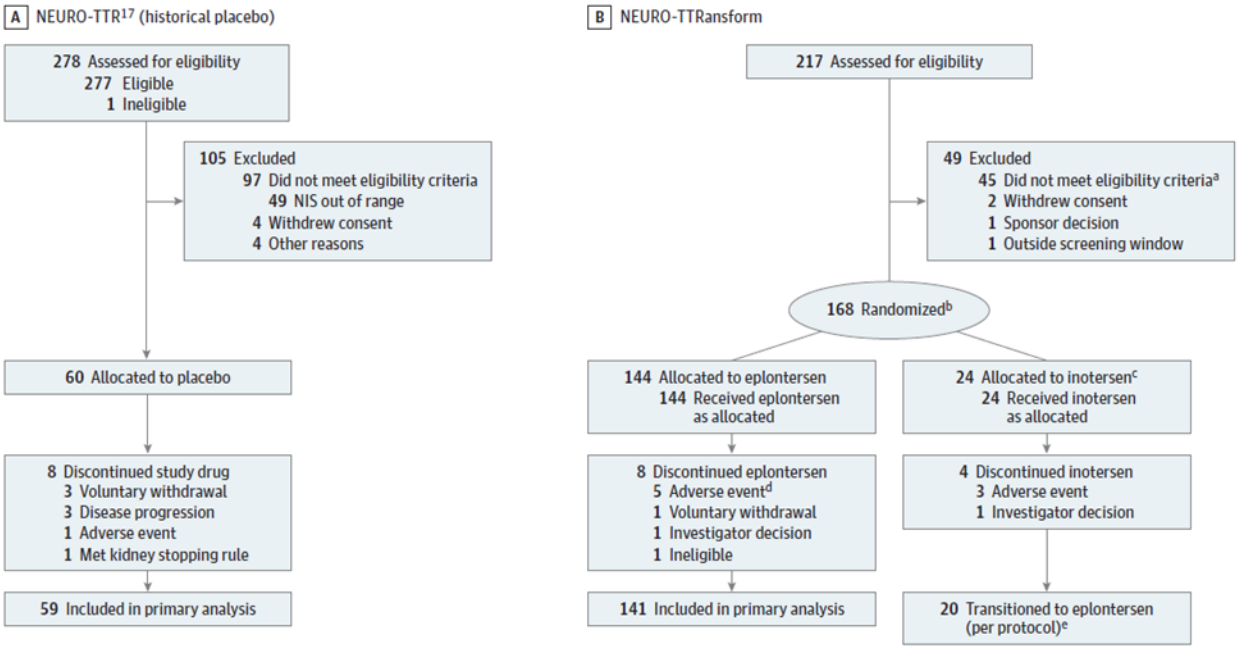
[g]In the historical placebo group, there were 2 cases of potential glomerulonephritis (1 glomerulonephritis chronic, 1 nephrotic syndrome). h Defined as TEAEs, with preferred terms containing the text "injection site." i Defined as TEAEs, with the preferred terms "influenza-like illness" or "pyrexia" (or feeling hot or body temperature increased), plus at least 1 of chills,myalgia, arthralgia, malaise, fatigue, headache, nausea.

[j]TEAE within the Standardized MedDRA (Medical Dictionary of Regulatory Activities) Query: drug-related hepatic disorders–comprehensive search.

[k]Both deaths consistent with known sequelae of hereditary transthyretin (ATTRv) amyloidosis. One patient with known ATTRv cardiomyopathy experienced a fatal cardiac arrhythmia after 4 doses of eplontersen, and 1 patient died of intracerebral hemorrhage after 10 doses of eplontersen (platelet counts and coagulation parameters within normal limits). One additional death occurred after the week-66 analysis; a patient with known ATTRv cardiomyopathy experienced a fatal myocardial infarction after 19 doses of eplontersen (death considered unrelated to study treatment).

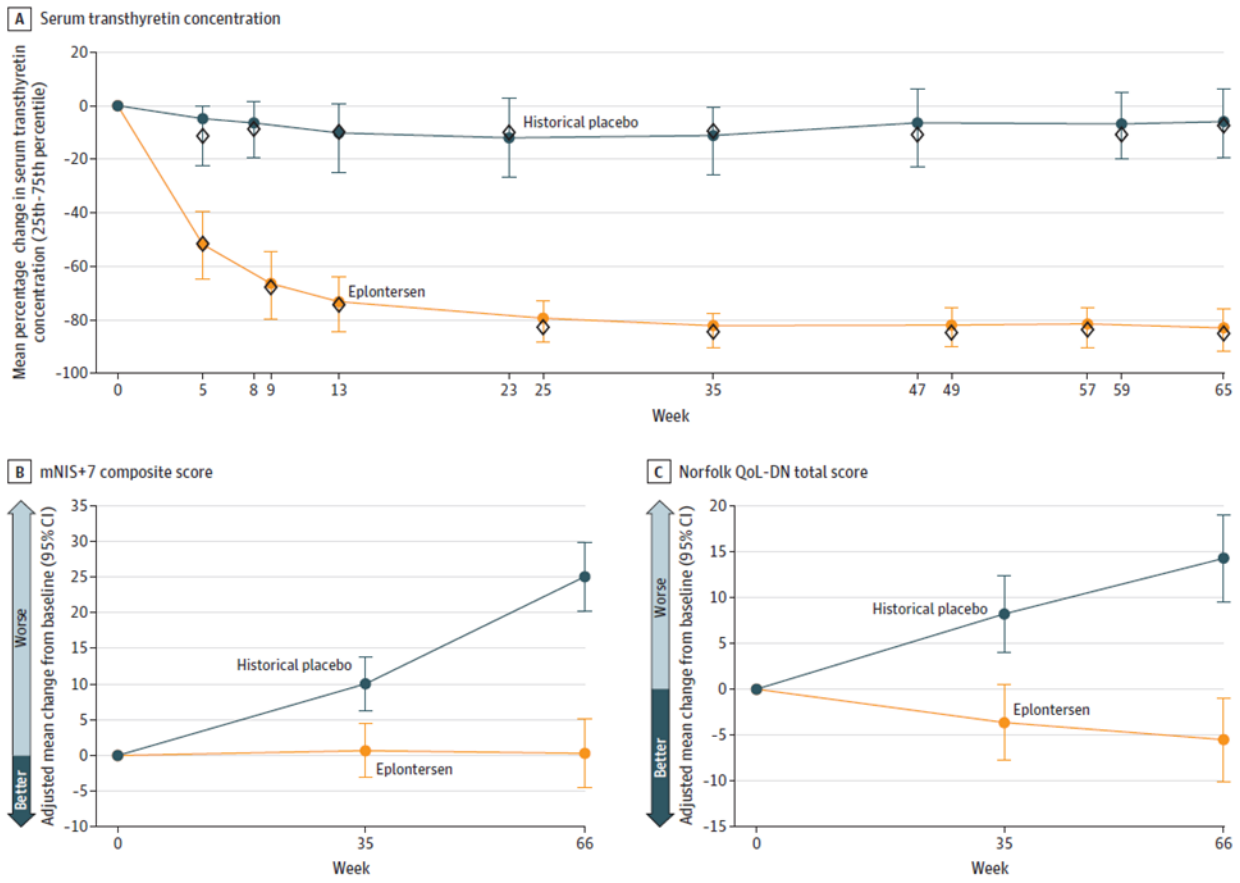
**Figures**

**Figure 1**. Recruitment, Randomization, and Patient Flow in the NEURO-TTRansform Trial



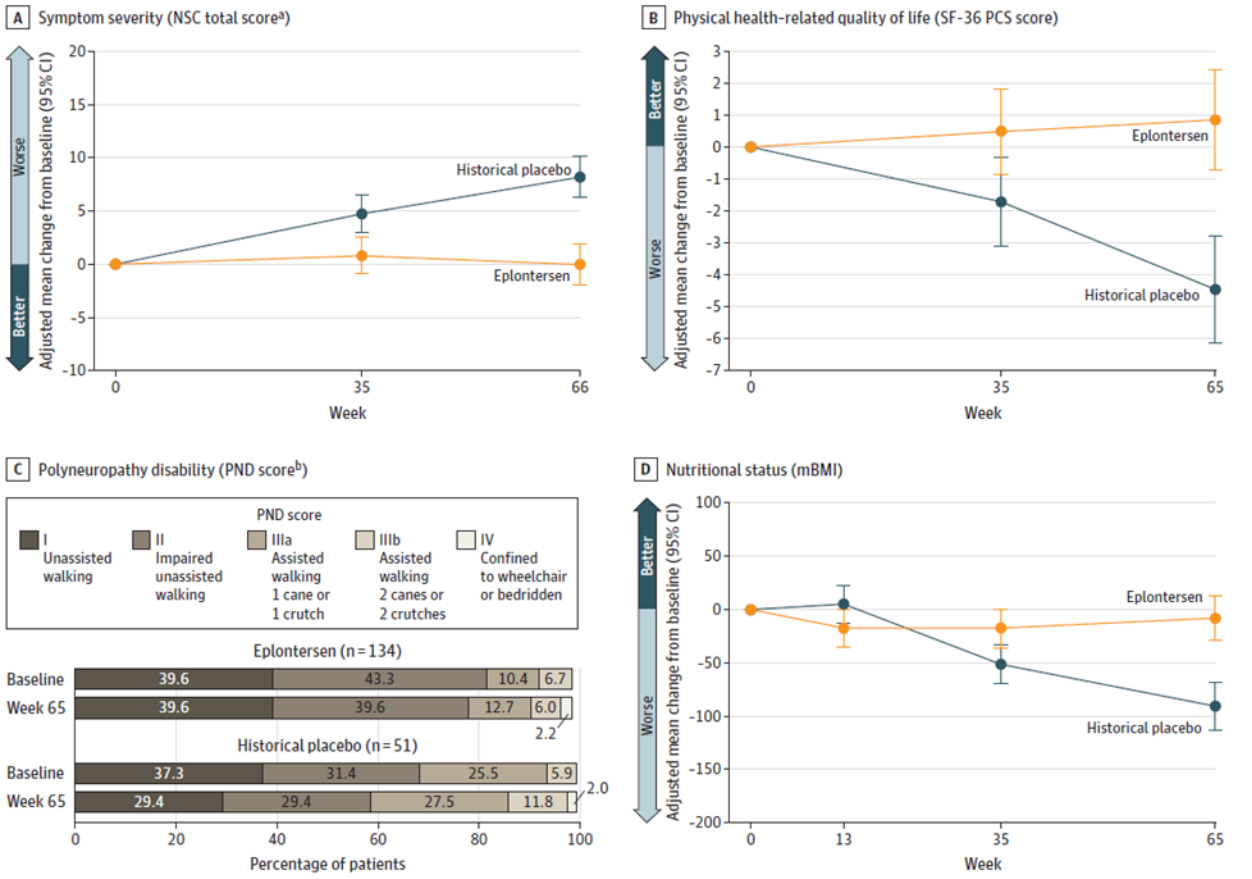

[a]Specific reasons for not meeting eligibility criteria (patients could have had >1 reason) included not meeting minimum criteria for signs and symptoms of hereditary transthyretin (ATTRv) amyloidosis (n = 13); urinalysis positive for blood (n = 5); serum vitamin A/retinol level less than lower limit of normal (n = 5); no documented genetic mutation in TTR gene (n = 5); platelet count less than 125 × 109/L (n = 3); known history of or positive test result for HIV, hepatitis C, or chronic hepatitis B (n = 2); urine protein to creatinine ratio 1000mg/g or greater (n = 2); monoclonal gammopathy of unknown significance and/or immunoglobulin free light chain ratio less than 0.26 and greater than 1.65 (n = 2); history of bleeding, diathesis, or coagulopathy (n = 2); consent not given (n = 2); clinically significant abnormalities in medical history (n = 1); renal insufficiency (difference between cystatin C and creatinine estimated glomerular filtration rate <60 mL/min/1.73m2) (n = 2); bilirubin level greater than or equal to 1.5 times upper limit of normal (n = 1); active infection requiring systemic antiviral or antimicrobial therapy that would not be completed prior to study day 1 (n = 1); Karnofsky performance status 50% or less (n = 1); presence of known type 1 or type 2 diabetes mellitus (n = 1); no reason recorded (n = 1).
[b]Eligible patients were randomized 6:1 to receive eplontersen or inotersen, respectively, using an Interactive Voice/Web-Response system (IxRS, Almac).
[c]The inotersen reference group was included to confirm sufficiently comparable disease progression and treatment response patterns between NEURO-TTRansform and NEURO-TTR,17 the source of the historical placebo. A diagram showing recruitment, randomization, and patient flow for the NEURO-TTR inotersen and placebo groups has been published.17
[d]One additional patient discontinued study drug after week 66 due to a treatment-emergent adverse event that started before week 66.
[e]See eFigure 1 in Supplement 2 for study design relative to the inotersen reference group in NEURO-TTRansform.

**Figure 2**. Change From Baseline in Primary End Points (Serum Transthyretin Concentration, mNIS+7 Composite Score, Norfolk QoL-DN Total Score)




A, Means (filled circles), medians (open diamonds), and first and third quartiles (lower and upper ends of whiskers) for percentage changes from baseline in serum transthyretin concentration at each study visit. The adjusted mean difference between eplontersen and historical placebo at week 65 was −70.4% (95%CI, −75.2%to −65.7%; P < .001). B, Changes from baseline (adjusted means [filled circles] and 95%CIs [lower and upper ends of whiskers]) in the modified Neuropathy Impairment Score +7 (mNIS+7) composite score, which range from −22.3 to 346.3, with higher scores indicating poorer function.26 The adjusted mean difference between eplontersen and historical placebo at week 66 was −24.8 (95%CI, –31.0 to −18.6; P < .001). C, Changes from baseline (adjusted means [filled circles] and 95%CIs [lower and upper ends of whiskers]) in Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QoL-DN) total score, which range from −4 to 136, with higher scores indicative of poorer quality of life.17 The adjusted mean difference between eplontersen and historical placebo at week 66 was –19.7 (95%CI, –25.6 to –13.8; P < .001). For the mNIS+7 composite score and Norfolk QoL-DN total score, a decrease in score indicates improvement. Data point values can be found in eTable 6 in Supplement 2.

**Figure 3**. Change From Baseline in Secondary End Points (NSC Total Score, SF-36 PCS Score, Distribution of Polyneuropathy Disability Scores at Baseline and Week 65, mBMI)




The difference between eplontersen and historical placebo in Neuropathy Symptom and Change (NSC) score at week 66 was –8.2 (95%CI, –10.7 to –5.8; P < .001). The difference between eplontersen and historical placebo in SF-36 score at week 65 was 5.3 (95%CI, 3.2-7.4; P < .001). The proportion of patients who could walk without assistance (polyneuropathy disability [PND] 1) remained at 39.6%in the eplontersen group and decreased from 37.3%to 29.4%in the historical placebo group. The difference between eplontersen and historical placebo in modified body mass index (mBMI) at week 65 was 82.7 $kg/m^2 \times g/L$ (95%CI, 54.6-110.8; P < .001). See eFigure 12 in Supplement 2 for individual contributions of changes in body mass index (BMI) and albumin to changes in mBMI. Data point values for panels A, B, and D are reported in eTable 7 in Supplement 2. SF-36 PCS indicates 36-Item Short Form Survey physical component summary.

[a]Change from baseline in NSC total score at week 35 was also assessed in the final analysis (difference between eplontersen and historical placebo at week 35: −3.9 [95%CI, −6.1 to −1.8; P < .001]).

[b]Percentages for patients with both baseline and week 65 values. The prespecified analysis of change from baseline in PND score vs historical placebo at week 65 was statistically significant (P < .05).