Supplementary Appendix 2

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NEURO-TTRansform Data and Safety Monitoring Board Members

Richard Becker, MD – Chair[a]	Cincinnati, Ohio, USA
Walter Bradley, DM, FRCP – Chair[a]	Miami, Florida, USA
Barry Greenberg, MD	La Jolla, California, USA
Willis Maddrey, MD	Dallas, Texas, USA
Bruce Molitoris, MD	Indianapolis, Indiana, USA
Lee-Jen Wie, PhD	Boston, Massachusetts, USA

[a]Dr Walter Bradley was Chair from November 2019 to June 2022; thereafter Dr Richard Becker served as Chair through 2023.

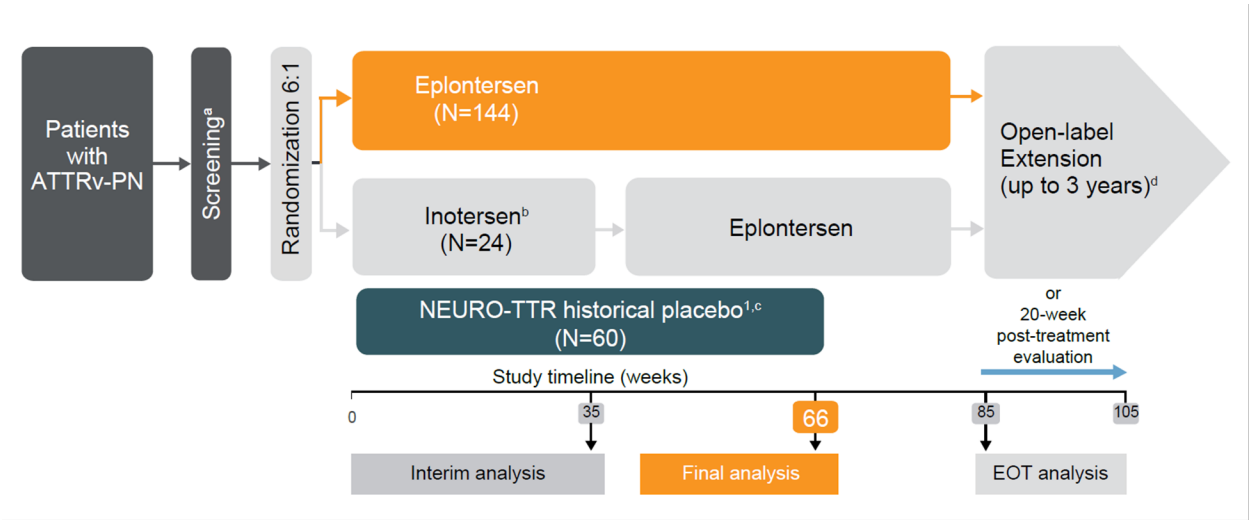
eAppendix 1. Propensity scoring.

The 3 clinically important factors with the highest potential of affecting efficacy in this population are disease stage, V30M variant, and previous treatment. It was therefore a priority to enroll patients with similar characteristics in the NEURO-TTRansform study as those in the NEURO-TTR study, especially for the above 3 factors. As a result, the patients in the eplontersen treatment group are similar to those in the historical placebo group from the NEURO-TTR study (Table 1 and eTable 3). Small differences between the historical placebo and eplontersen groups were observed and accounted for by propensity score adjustment. The propensity score was calculated for each patient using a logistic regression model with covariates including disease stage (Stage 1/Stage 2), V30M variant (Yes/No), and previous treatment with tafamidis or diflunisal (Yes/No) (eFigure 3). The comparative efficacy analysis using the mixed effects model with repeated measures was conducted using inverse probability weights based on propensity scores.

eAppendix 2. Impact of COVID-19 on NEURO-TTRansform.

Mitigation efforts (eg, virtual visits, increased scheduling flexibility, remote consent) enabled the trial to be conducted despite the COVID-19 pandemic and ensured the safety of participants and the integrity of the data. The pandemic did not appear to have a clinically meaningful impact on monitoring and data collection or interpretation of the efficacy and safety results. Up to week 66, a total of 35 patients in the eplontersen group had an adverse event of COVID-19, 2 patients had an adverse event of COVID-19 pneumonia, and 1 patient had an adverse event of asymptomatic COVID-19 during the trial. There were no discontinuations in the eplontersen group due to COVID-19. Because the historical placebo group was from a trial conducted prior to the pandemic, there was no impact of COVID-19 on historical placebo data.

eFigure 1. NEURO-TTRansform study design.



[a]The screening period is ≤ 6 weeks (or ≤ 10 weeks if genetic testing is required).

[b]The inotersen reference group was included to confirm sufficiently comparable disease progression and treatment response patterns between NEURO-TTR[1] (NCT01737398) and NEURO-TTRansform.

[c]Placebo arm of the NEURO-TTR trial.[1]

[d]Patients not participating in the open-label extension will enter a 20-week post-treatment evaluation after completing EOT assessments.

ATTRv, hereditary transthyretin; EOT, end of treatment.

eFigure 2. Components and scoring of NIS and mNIS scales used in ATTRv polyneuropathy clinical trials.[2]

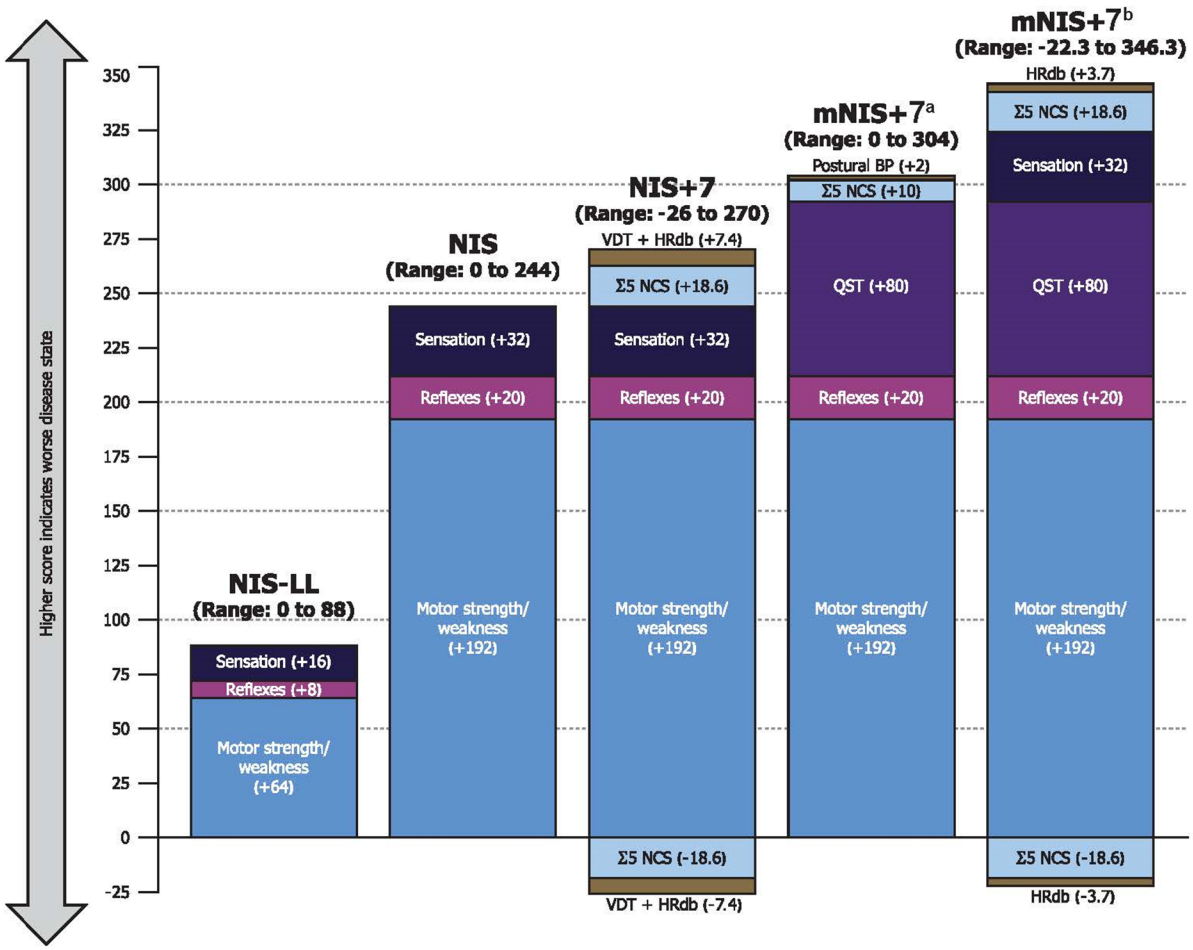


Figure adapted and reprinted from Dyck et al, *J Neurol Sci*, 405:116424, 2019,[2] with permission from Elsevier.

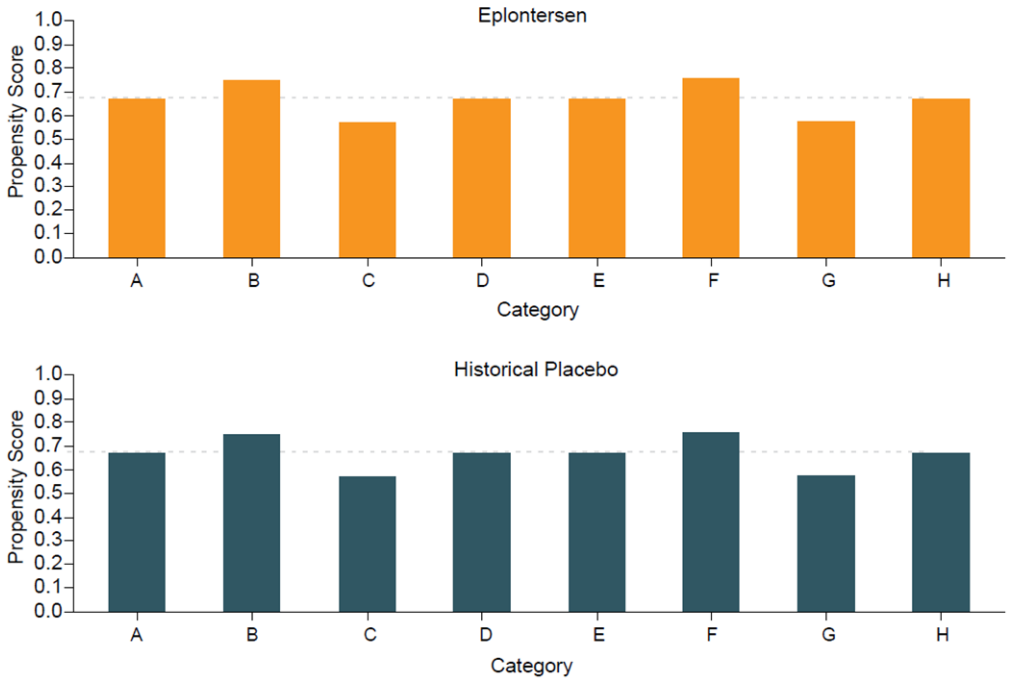
[a]Used in the phase 3 APOLLO trial of patisiran and the phase 3 HELIOS-A trial of vutrisiran.[3,4]

[b]Used in this trial, as well as the phase 3 NEURO-TTR trial of inotersen.[1]

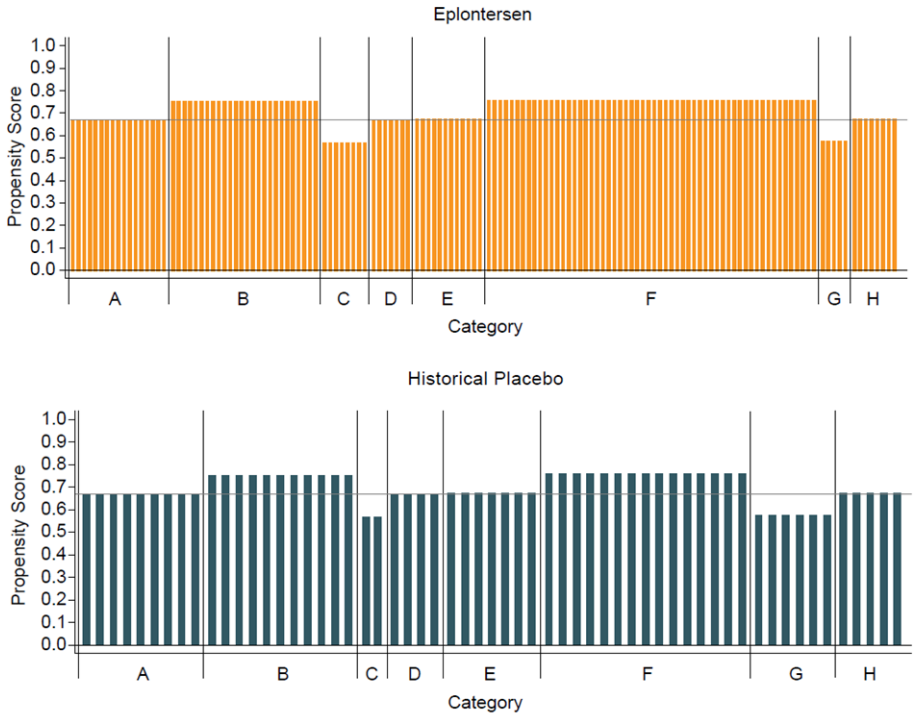
ATTRv, hereditary transthyretin; BP, blood pressure; HRdb, heart rate with deep breathing; mNIS, modified Neuropathy Impairment Score; mNIS+7, modified Neuropathy Impairment Score+7; NCS, nerve conduction studies; NIS, Neuropathy Impairment Score; NIS+7, Neuropathy Impairment Score+7; NIS-LL, Neuropathy Impairment Score - lower limb; QST, quantitative sensation testing; VDT, vibration detection threshold.

eFigure 3. Propensity score from the logistic regression model of serum TTR (g/L) at week 65 (full analysis set) group results (A) and individual results (B).

A



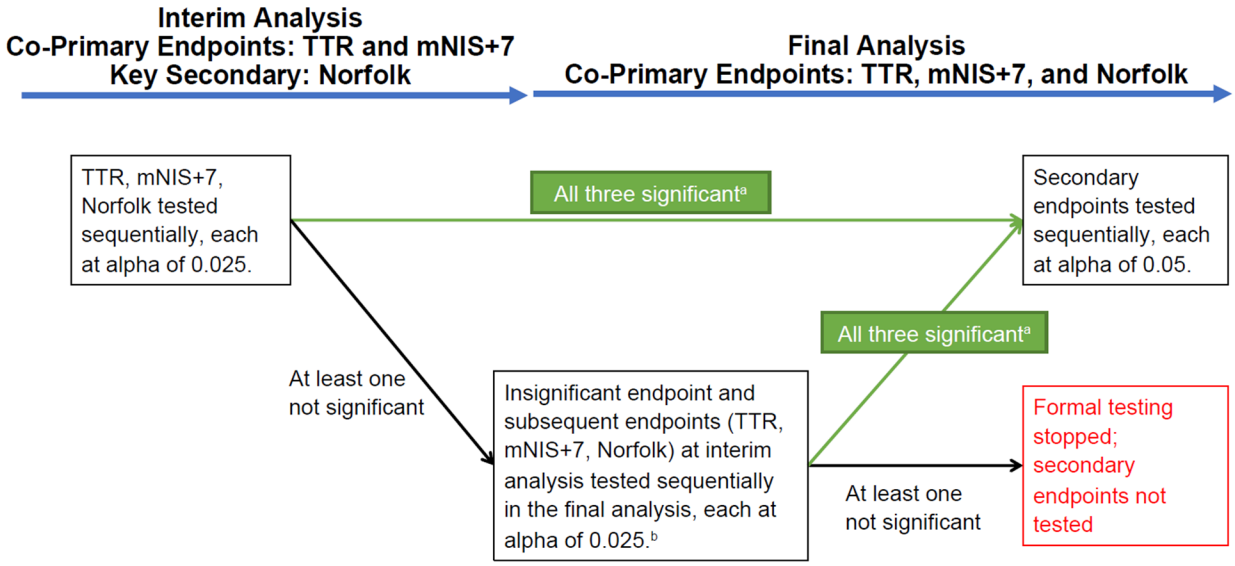
B



Category	Previous treatment with tafamidis or diflunisal	*TTR* variant, V30M	Coutinho stage Stage 1 (ambulatory without assistance) Stage 2 (ambulatory with assistance)
A	No	No	Stage 1
B	Yes	No	Stage 1
C	No	No	Stage 2
D	Yes	No	Stage 2
E	No	Yes	Stage 1
F	Yes	Yes	Stage 1
G	No	Yes	Stage 2
H	Yes	Yes	Stage 2

The horizontal line at 0.667 represents the propensity score in a perfectly balanced distribution for 2:1 ratio design.

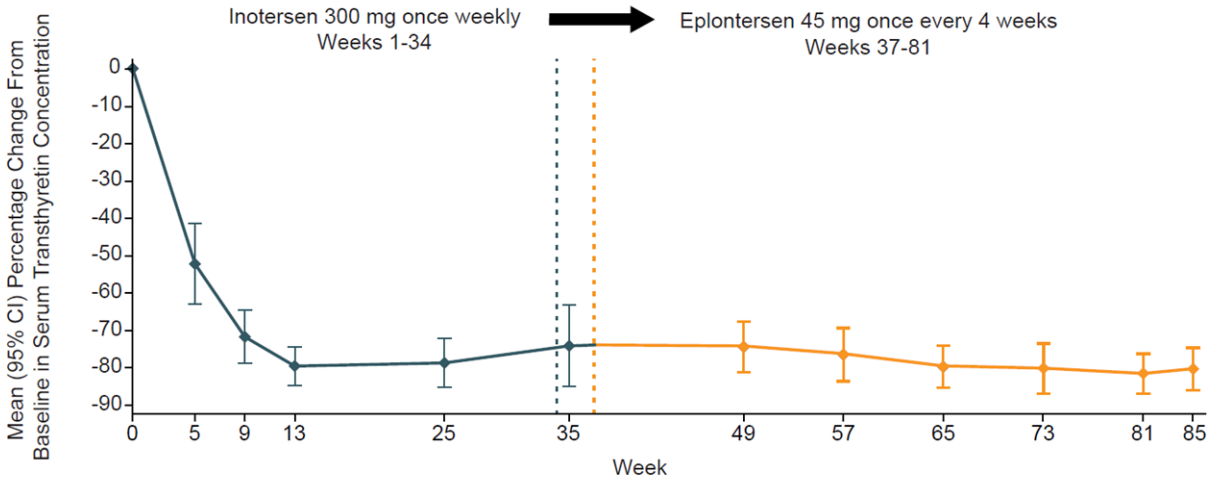
eFigure 4. Hierarchical testing procedure for the interim and final analyses.



[a]The study will be considered positive if, at the interim analysis at week 35, both co-primary endpoints, TTR and mNIS+7, are statistically significant. If the study is not positive at the interim analysis, it will still be considered positive if all 3 co-primary endpoints, TTR, mNIS+7, and Norfolk, are statistically significant at the final analysis at week 66.

[b]The alpha level of 0.025 for each primary endpoint tested at final analysis can be improved by using the resampling procedure, which incorporates the correlation between the 2 test statistics from the interim analysis and the final analysis.[5]

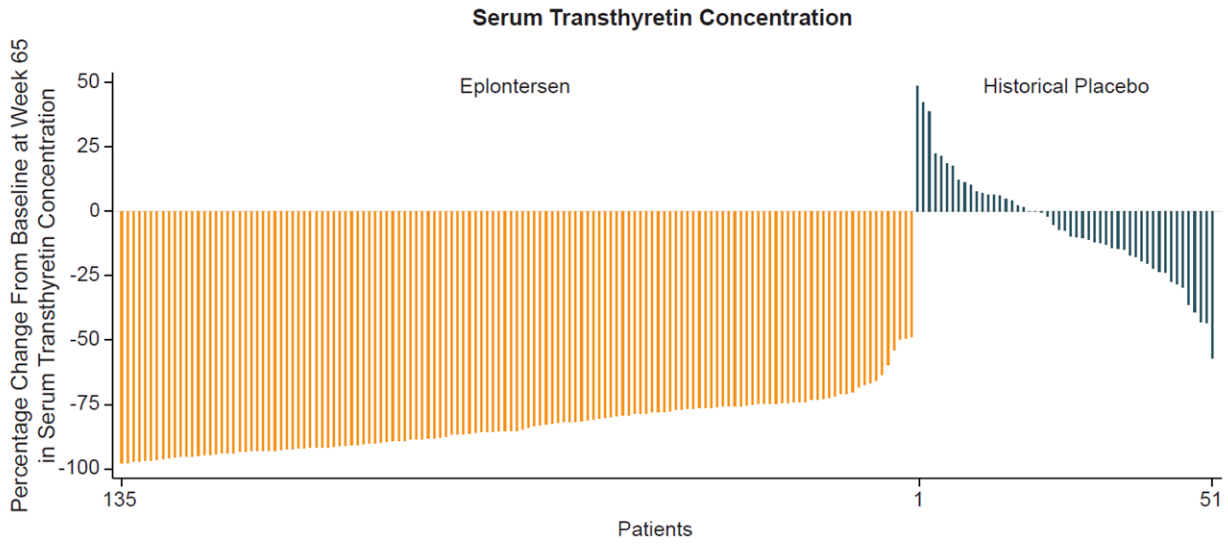
eFigure 5. Change in serum transthyretin concentration in patients randomized to inotersen who transitioned to eplontersen treatment in NEURO-TTRansform.



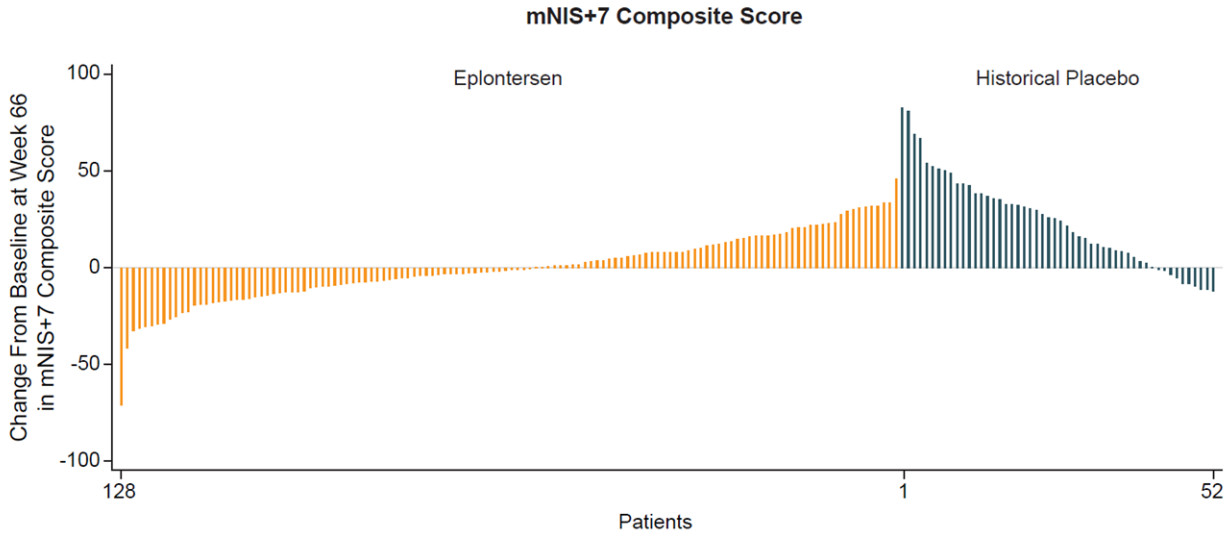
Vertical dark blue dashed line represents last dose of inotersen received at week 34. Vertical yellow dashed line represents first dose of eplontersen received at week 37.

eFigure 6. Parallel line plots of percentage change from baseline in serum transthyretin at week 65 (A), change from baseline in mNIS+7 composite score at week 66 (B), and change from baseline in Norfolk QoL-DN total score at week 66 (C).

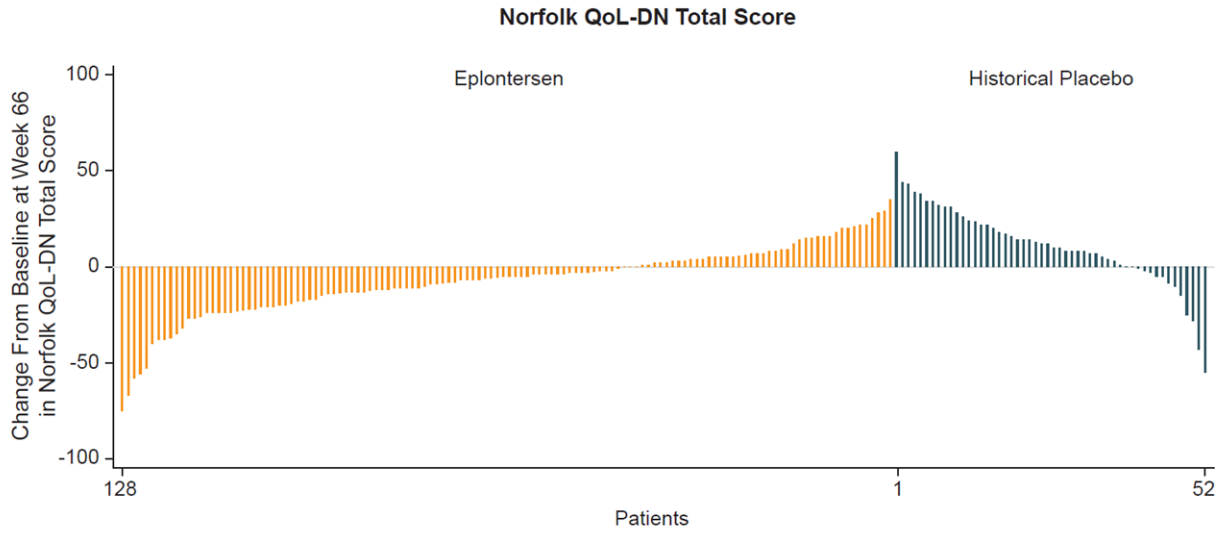
A



B



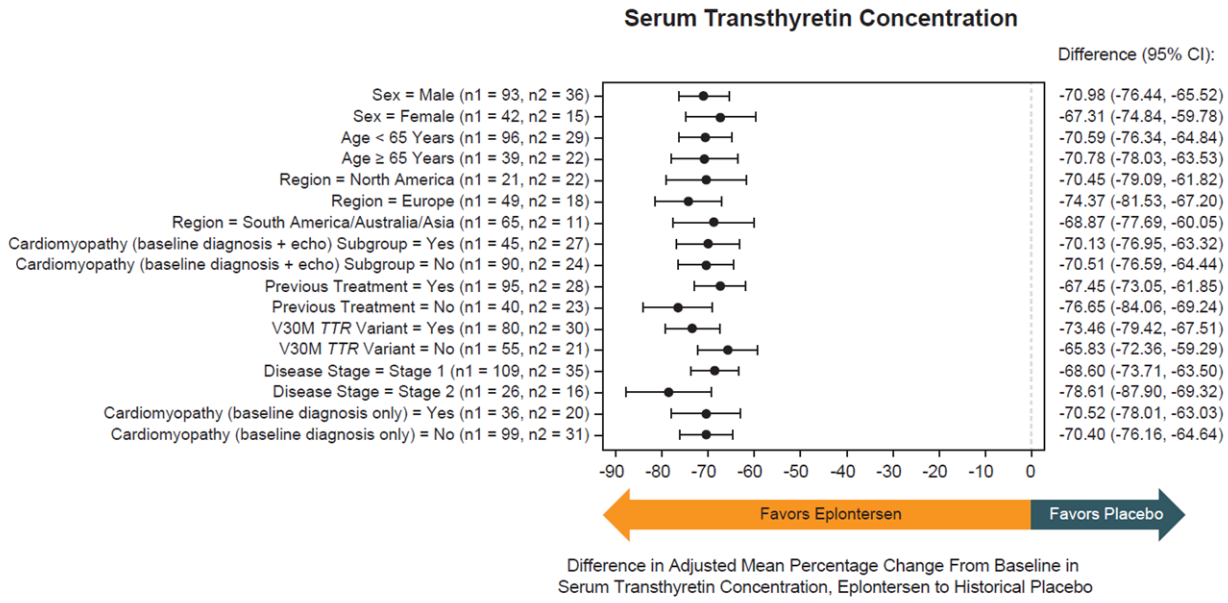
C



mNIS+7, modified Neuropathy Impairment Score+7; QoL-DN, Quality of Life–Diabetic Neuropathy.

eFigure 7. Treatment effect on percentage change from baseline in serum transthyretin concentration at week 65 (A), change from baseline in mNIS+7 composite score at week 66 (B), and change from baseline in Norfolk QoL-DN total score at week 66 (C) by subgroup.

A



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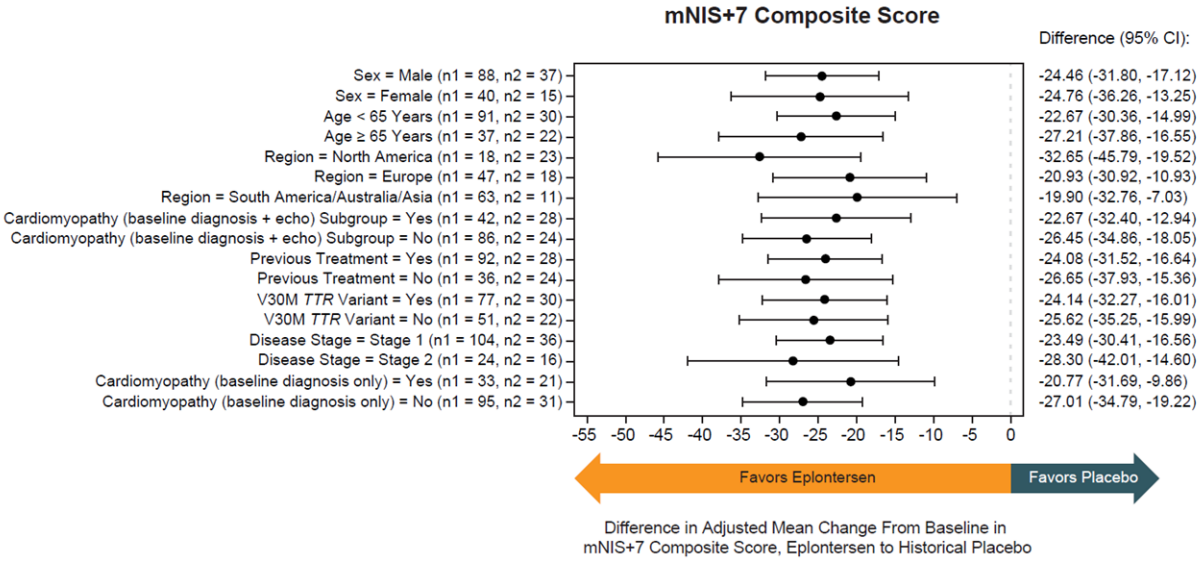
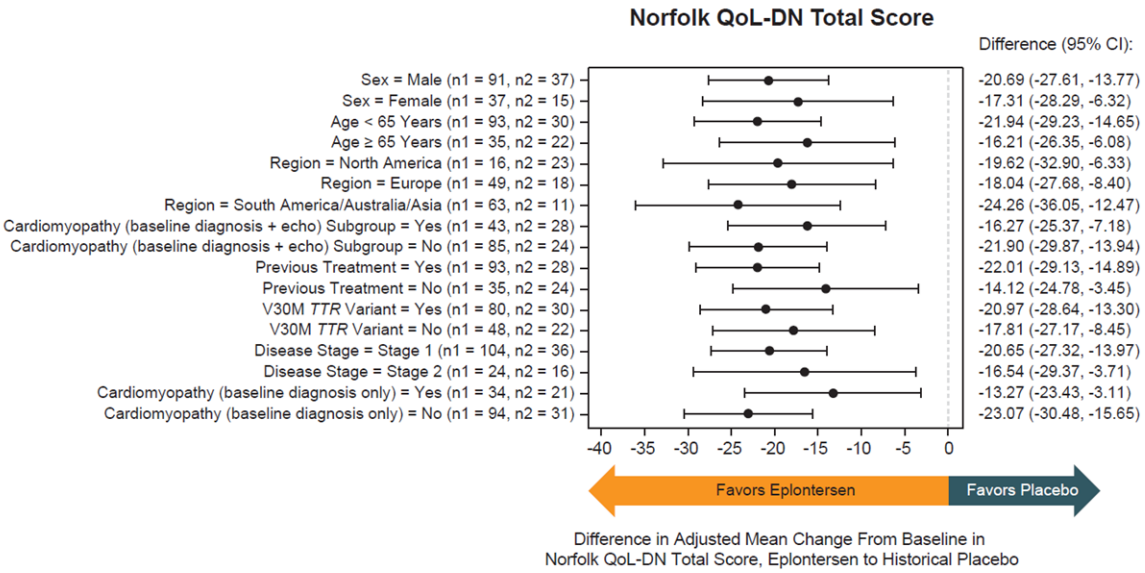


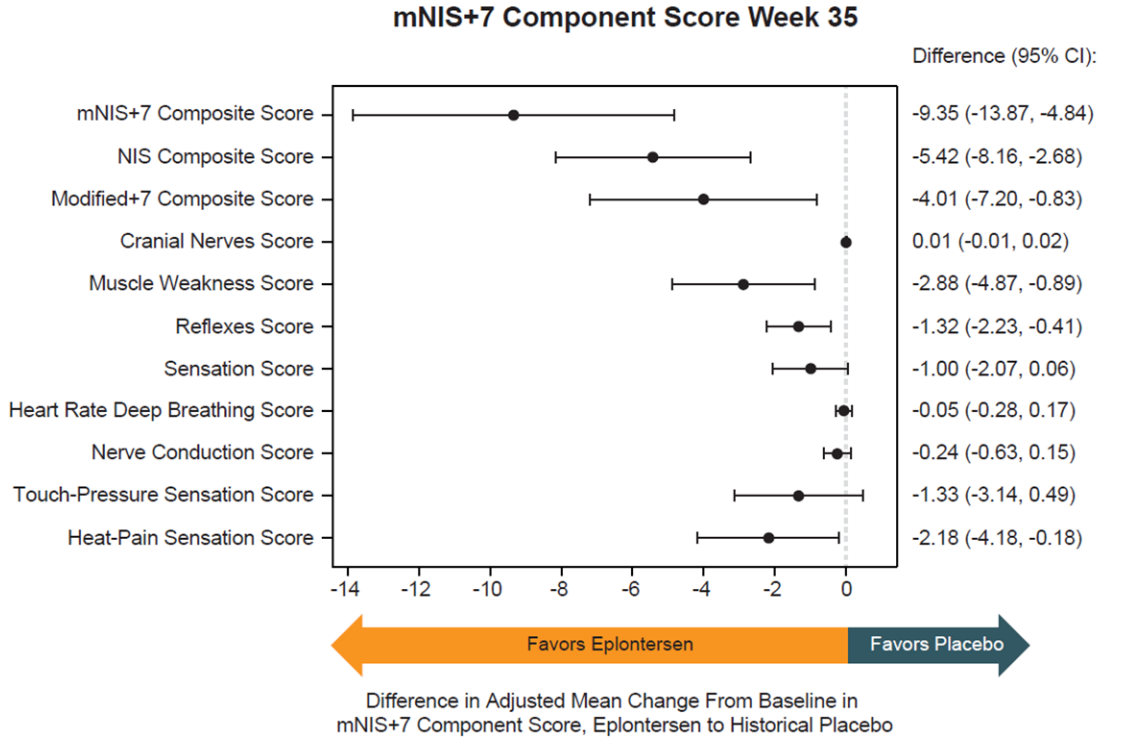
C

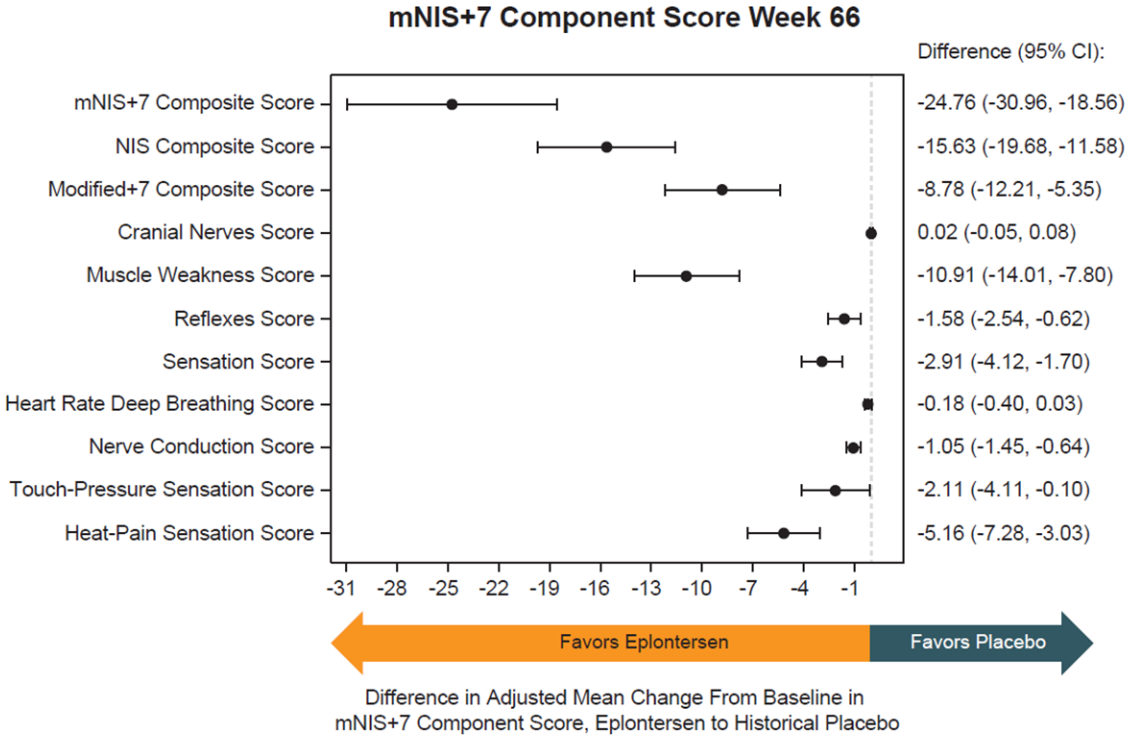


Echo, echocardiography; mNIS+7, modified Neuropathy Impairment Score+7; n1, number of patients in eplontersen group; n2, number of patients in historical placebo group; QoL-DN, Quality of Life–Diabetic Neuropathy.

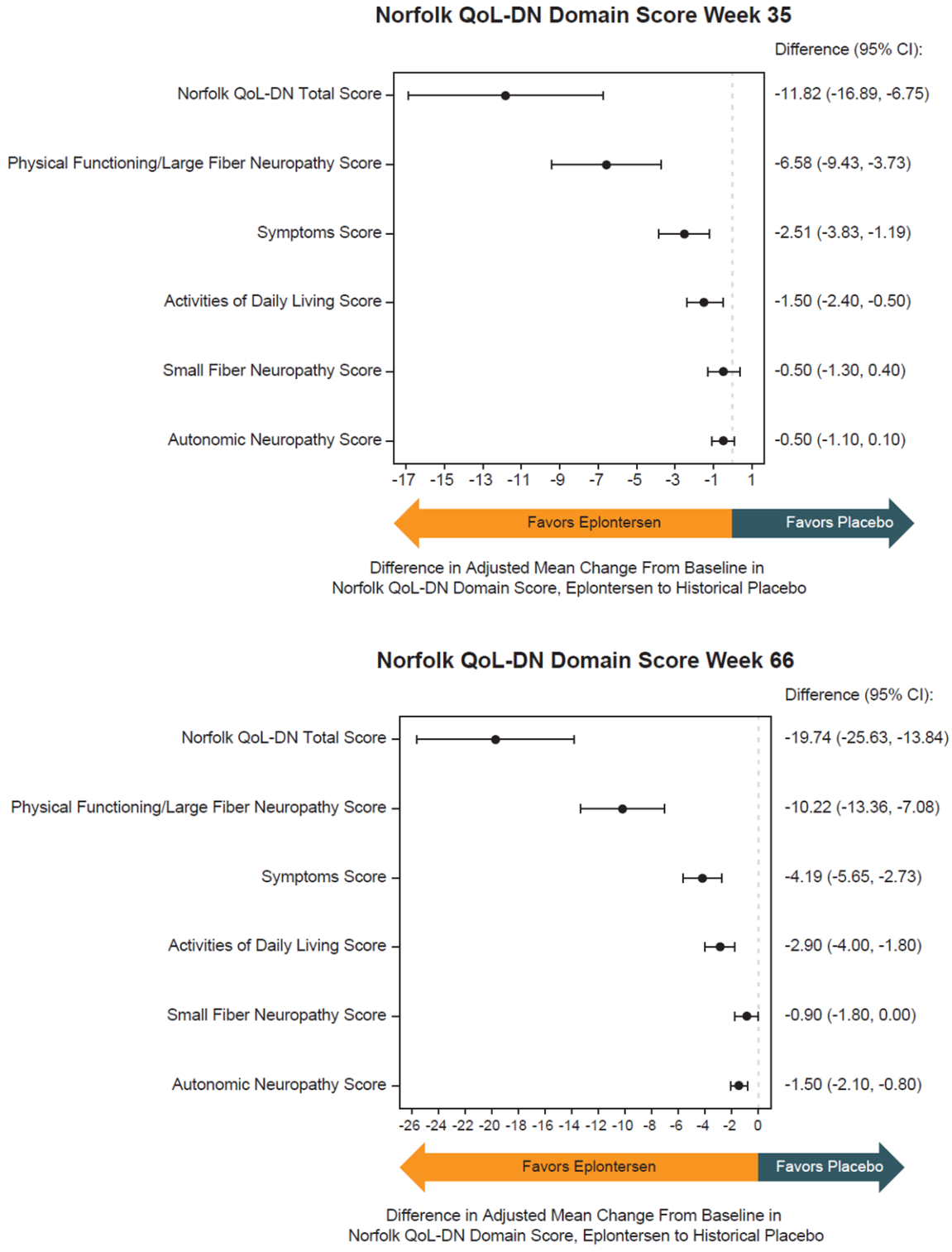
eFigure 8. Treatment effect on (A) mNIS+7 component scores and (B) Norfolk QoL-DN domain scores.

A





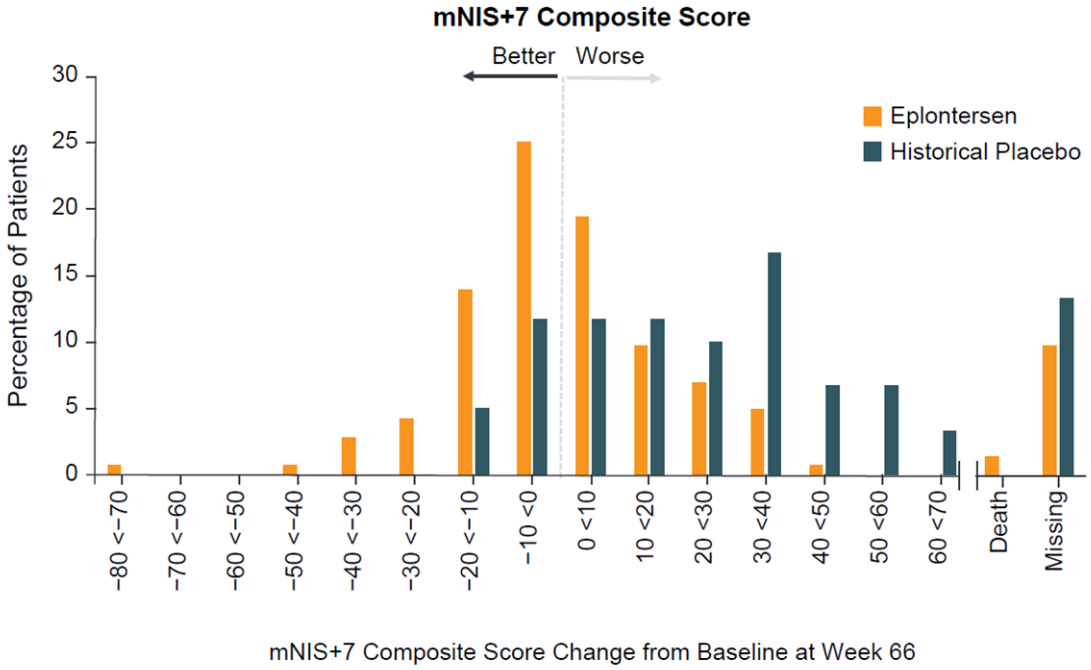
B



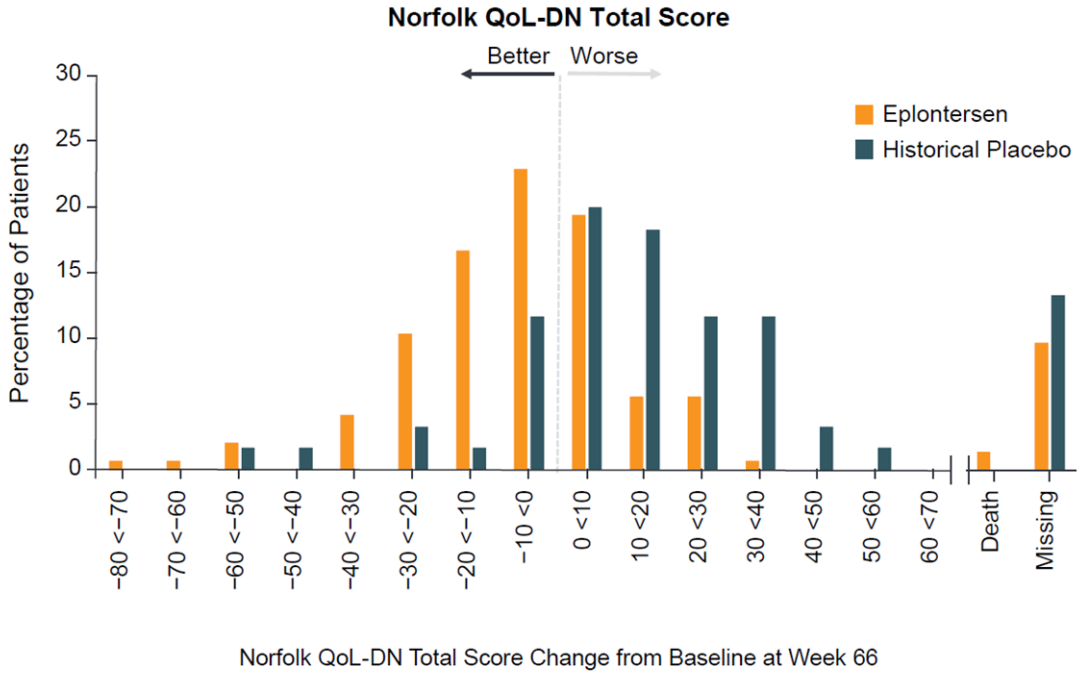
mNIS+7, modified Neuropathy Impairment Score+7; NIS, Neuropathy Impairment Score; QoL-DN, Quality of Life–Diabetic Neuropathy.

eFigure 9. Change from baseline at week 66 in (A) mNIS+7 composite score and (B) Norfolk QoL-DN total score.

A



B

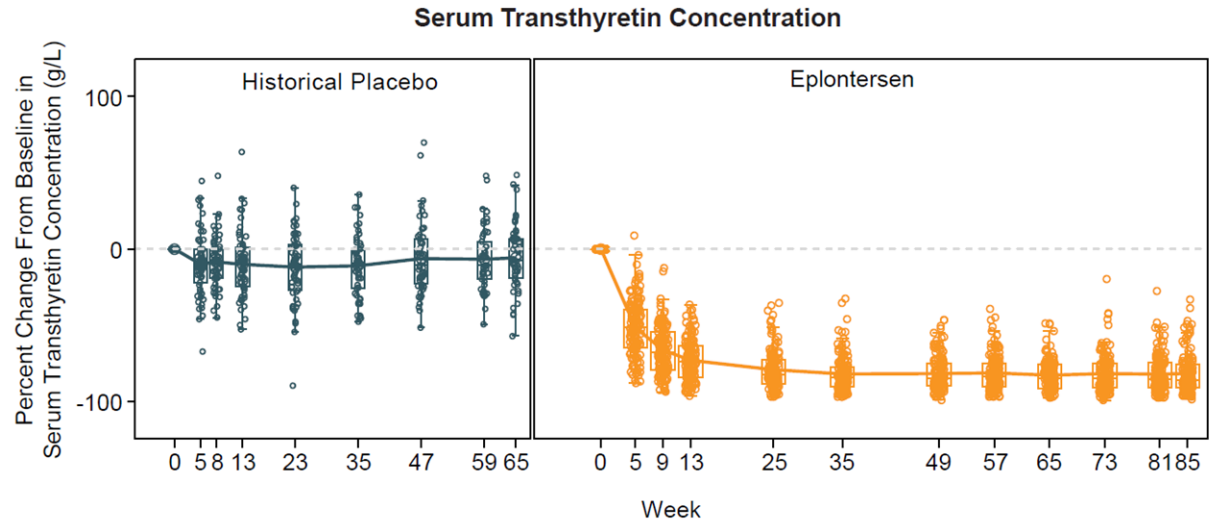


Plots depict 10-point categories for change from baseline. The percentages of patients were calculated using the safety analysis population as the denominator.

mNIS+7, modified Neuropathy Impairment Score+7; QoL-DN, Quality of Life–Diabetic Neuropathy.

eFigure 10. Efficacy outcomes at week 85: serum transthyretin concentration (A), mNIS+7 composite score (B), and Norfolk QoL-DN total score (C).

A[a]



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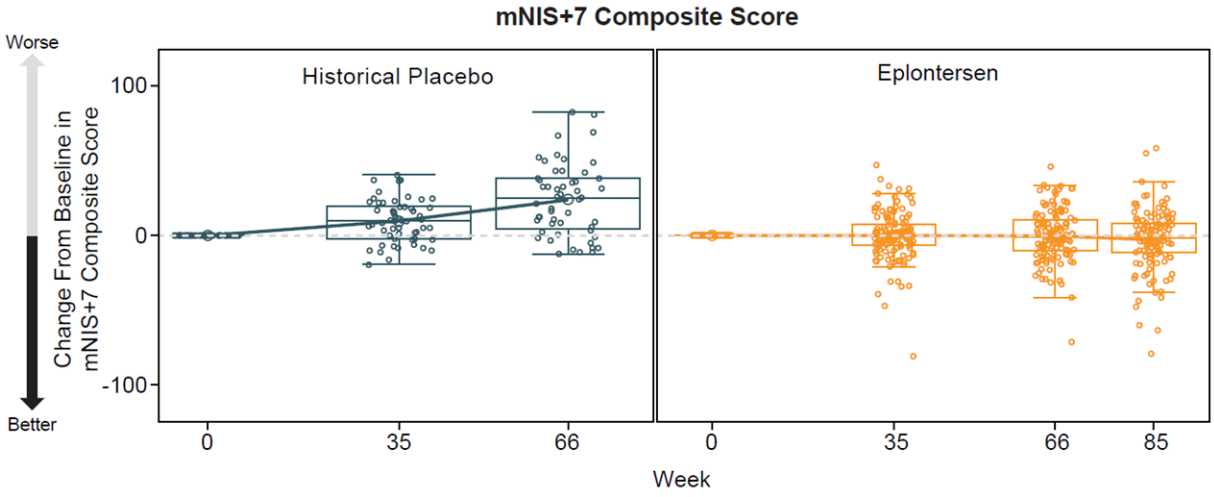
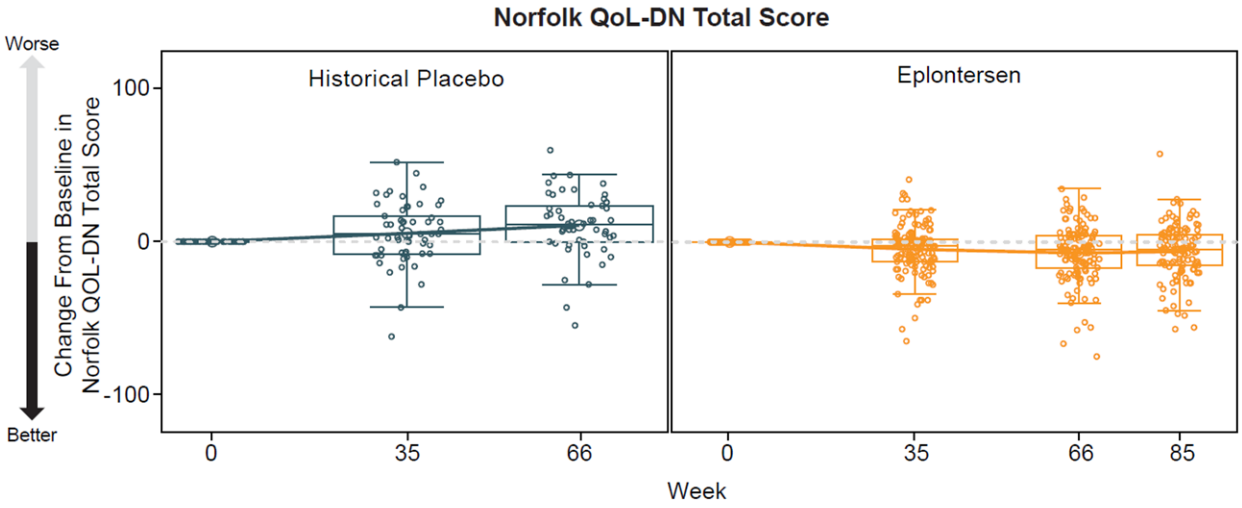


C



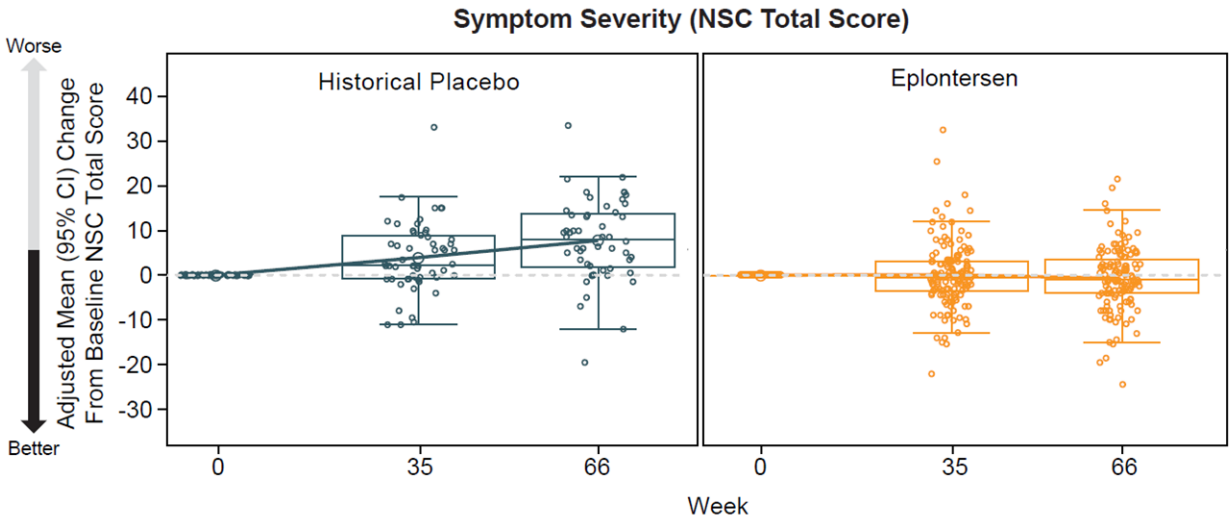
[a]Historical placebo patients with percent change from baseline > 100% (296.0% at Week 5 and 120.4% at Week 8) are excluded from the plot.

Solid line = mean values

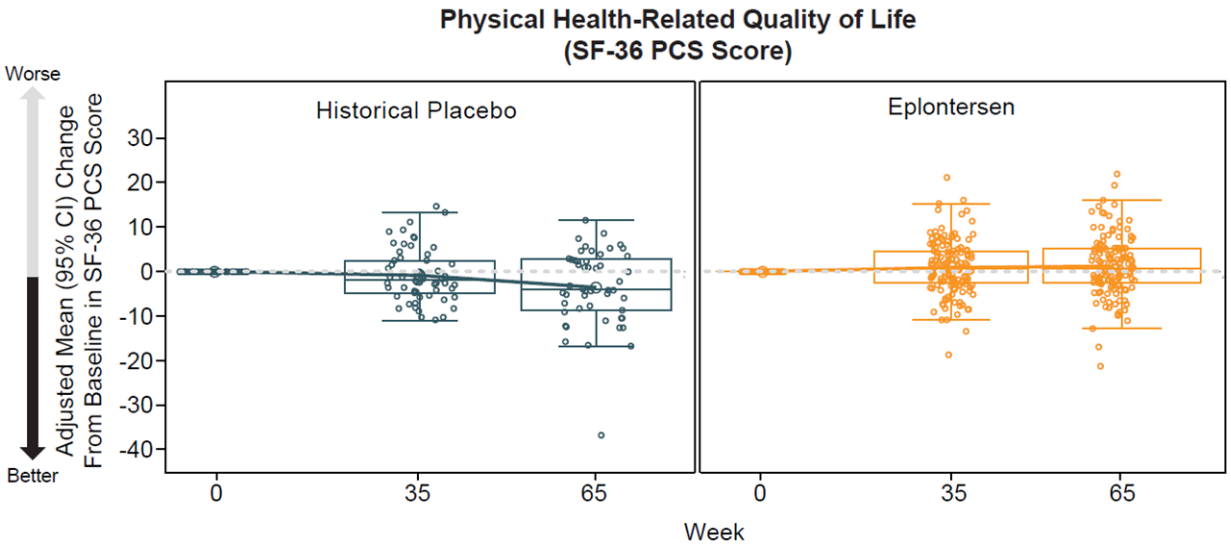
mNIS+7, modified Neuropathy Impairment Score+7; QoL-DN, Quality of Life–Diabetic Neuropathy.

eFigure 11. Secondary efficacy outcomes. NSC Total Score at week 66 (A), SF-36 PCS Score at week 65 (B), and mBMI at week 65 (C).

A



B



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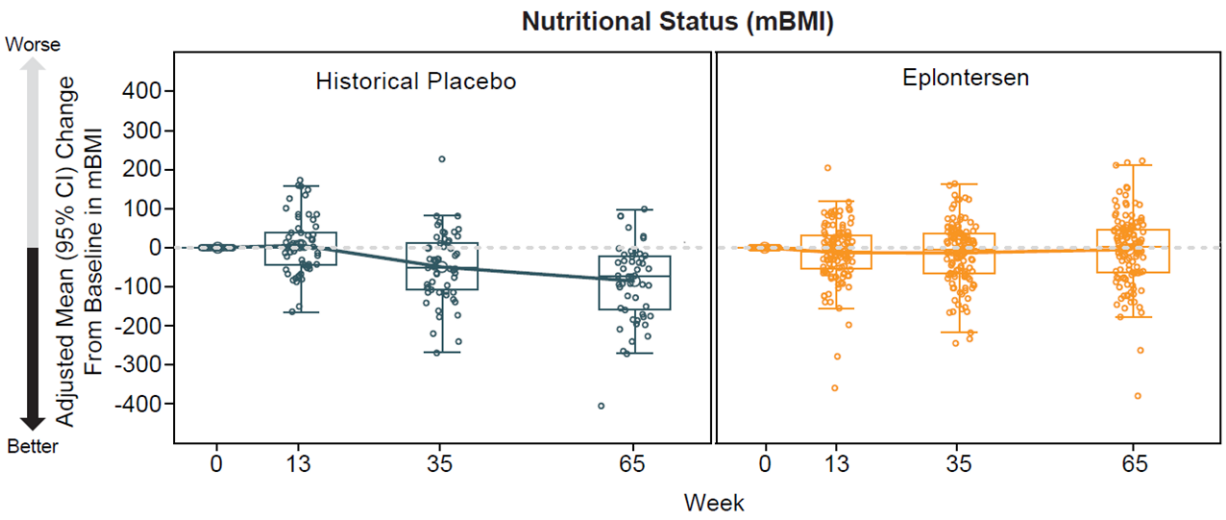
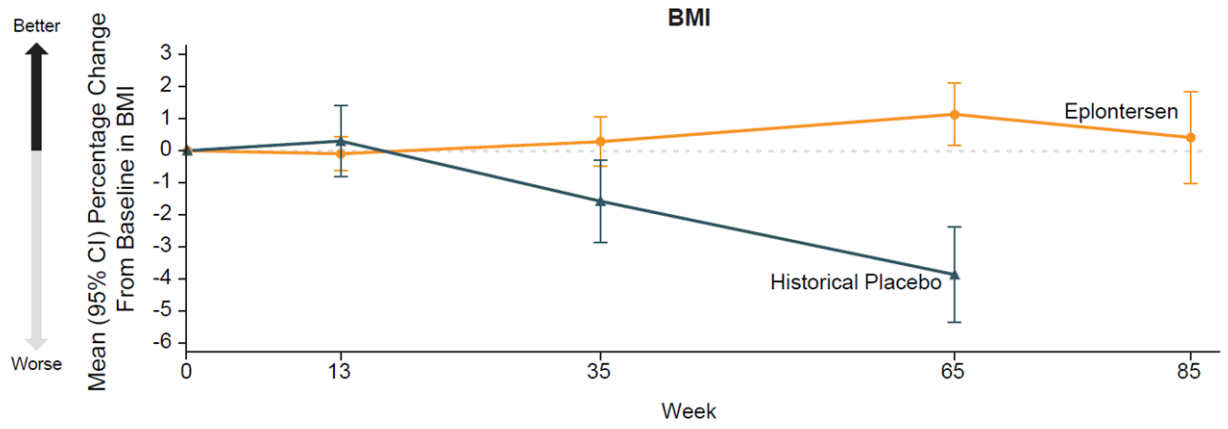


Solid line = mean values

CI, confidence internal; mBMI; modified body mass index; NSC, neuropathy symptom and change; SF-36 PCS, 36-Item Short Form Survey physical component summary.

eFigure 12. Change from baseline in BMI (A) and albumin (B).

A



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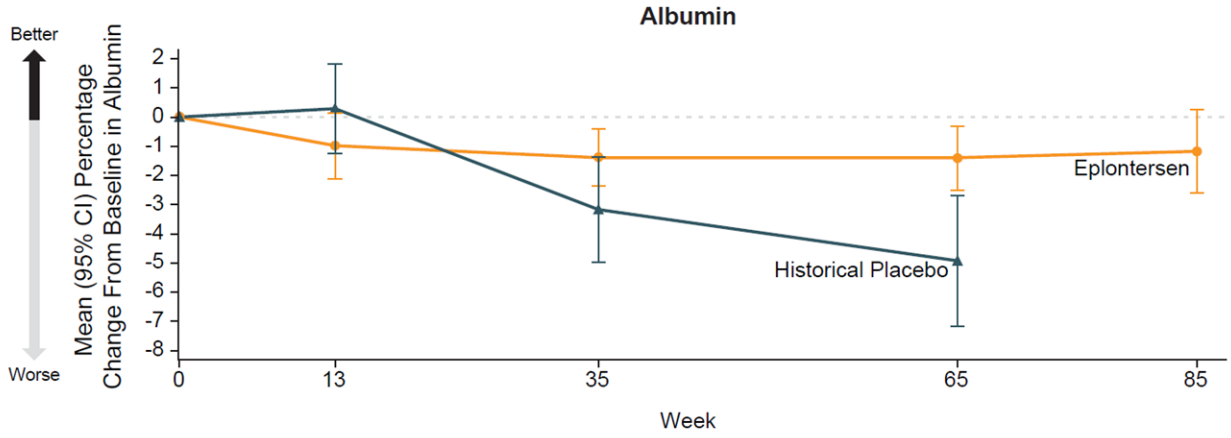

BMI, body mass index.

eTable 1. Prevalence of different *TTR* sequence variants.

***TTR* Variant**	**Eplontersen (N = 144)**	**Historical Placebo (N = 60)**
V30M	85 (59)	33 (55)
A97S	21 (15)	1 (2)
T60A	4 (3)	8 (13)
L58H	4 (3)	3 (5)
S77Y	3 (2)	5 (8)
F64L	5 (3)	3 (5)
S50R	2 (1)	1 (2)
E89Q	1 (1)	0
V122I	4 (3)	1 (2)
T49A	1 (1)	0
Other	14 (10)[a]	5 (10)[b]

Data are No. (%).

[a]Other *TTR* variants observed in 1 patient each: E62D, A101V, A39D, p.I127M, E74Q, E54Q, E54G, V32A, F44S, I127V; other *TTR* variants observed in 2 patients each: I107V, G47A.

[b]Other *TTR* variants observed in 1 patient each: D38A, E54S, E61K, G47A, K35T.

eTable 2. Patient demographics and baseline clinical characteristics of NEURO-TTRansform and NEURO-TTR[1] treatment groups.

Characteristic	NEURO-TTRansform		NEURO-TTR	
	Eplontersen (N = 144)	**Inotersen (reference) (N = 24)**	**Inotersen (N = 112)**	**Placebo[a] (N = 60)**
Age, yr, mean (SD)	53.0 (15.0)	51.1 (14.4)	59.0 (12.5)	59.5 (14.0)
Sex, n (%)				
Female	44 (31)	8 (33)	35 (31)	19 (32)
Male	100 (69)	16 (67)	77 (69)	41 (68)
Race, n (%)	*n = 143*	*n = 23*		
Asian	22 (15)	2 (9)	1 (1)	3 (5)
Black or African American	5 (3)	0	3 (3)	1 (2)
White	112 (78)	19 (83)	105 (94)	53 (88)
Other or multiple	4 (3)	2 (9)	3 (3)	3 (5)
Geographic region, n (%)				
North America	21 (15)	5 (21)	56 (50)	26 (43)
Europe	54 (38)	10 (42)	37 (33)	23 (38)
South America/Australia/ New Zealand/Asia	69 (48)	9 (38)	19 (17)	11 (18)
Body weight, kg	*n = 141*	*n = 23*		
Mean (SD)	70.3 (15.8)	79.2 (19.3)	70.6 (17.0)	71.1 (18.1)
BMI, kg/m^2	*n = 138*	*n = 22*	*n = 111*	
Mean (SD)	24.4 (4.9)	26.4 (5.4)	24.0 (4.9)	24.2 (4.9)
Modified BMI, $kg/m^2 \times g/L$[b]	*n = 138*	*n = 22*	*n = 111*	
Mean (SD)	1025.8 (235.1)	1101.7 (246.5)	1010.9 (227.8)	1049.9 (228.4)
Albumin, g/L, mean (SD)	42.2 (2.9)	42.0 (2.7)	42.1 (3.3)	43.5 (3.1)

TTR variant, n (%) V30M Non-V30M	 85 (59) 59 (41)	 16 (67) 8 (33)	 56 (50) 56 (50)	 33 (55) 27 (45)
Coutinho stage, n (%) Stage 1 (ambulatory without assistance) Stage 2 (ambulatory with assistance)	 115 (80) 29 (20)	 18 (75) 6 (25)	 74 (66) 38 (34)	 42 (70) 18 (30)
Polyneuropathy disability score, n (%) I: Sensory disturbances, but preserved walking capability II: Impaired walking capability, but ability to walk without a stick or crutches IIIa: Walking only with the help of 1 stick or crutch IIIb: Walking with the help of 2 sticks or crutches IV: Confined to a wheelchair or bedridden	*n = 143* 56 (39) 61 (43) 16 (11) 10 (7) 0	 12 (50) 8 (33) 3 (13) 1 (4) 0	 32 (29) 42 (38) 30 (27) 8 (7) 0	 23 (38) 19 (32) 15 (25) 3 (5) 0
Previous treatment with tafamidis or diflunisal, n (%)	100 (69)	15 (63)	63 (56)	36 (60)
Duration of disease from diagnosis of ATTRv polyneuropathy,[c] mo, mean (SD)	46.8 (58.1)	45.7 (54.1)	42.4 (51.2)	39.3 (40.3)

Duration of disease from onset of symptoms of ATTRv polyneuropathy,[c] mo	*n = 143*			
Mean (SD)	67.7 (50.9)	72.5 (111.0)	63.9 (53.2)	64.0 (52.3)
ATTRv cardiomyopathy clinical diagnosis from CRF				
Cardiomyopathy baseline diagnosis-only, n (%)	39 (27)	7 (29)	45 (40)	22 (37)
Cardiomyopathy baseline diagnosis plus echocardiography,[d] n (%)	49 (34)	9 (38)	64 (57)	30 (50)
mNIS+7 composite score[e]				
Mean (SD)	81.3 (43.4)	65.1 (33.5)	79.2 (37.0)	74.8 (39.0)
Norfolk QoL-DN total score[f]	*n = 137*		*n = 111*	*n = 59*
Mean (SD)	44.1 (26.6)	40.1 (21.5)	48.2 (27.5)	48.7 (26.7)
NSC total score[g]				
Mean (SD)	23.1 (12.4)	20.6 (10.5)	24.8 (13.1)	23.0 (12.6)
SF-36 PCS score[h]			*n = 111*	
Mean (SD)	39.7 (9.3)	39.7 (9.6)	35.7 (8.7)	37.2 (9.8)

[a]Historical placebo in NEURO-TTRansform.

[b]Modified BMI was defined as body mass index in kg/m^2 × albumin level in g/L; higher scores are indicative of better nutritional status.

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

[d]Patients with 1) a clinical diagnosis of ATTRv cardiomyopathy on their CRF (i.e., the cardiomyopathy baseline diagnosis-only subgroup), or 2) interventricular septum thickness ≥ 13 mm 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 mmHg at any time during the trial (including screening and baseline visits).

[e]Composite scores on the mNIS+7 scale range from −22.3 to 346.3, with higher scores indicating poorer function.

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

[g]Total scores on the NSC range from 0 to 114 (men) or 108 (women), with higher scores indicating worse symptoms.

[h]Scores on the SF-36 PCS range from 0 to 100, with higher scores indicating better physical health-related quality of life.

Percentages may not total 100 due to rounding.

Q1, Q3 represent first and third quartiles.

ATTRv, hereditary transthyretin; BMI, body mass index; CRF, case report form; mNIS+7, modified Neuropathy Impairment Score+7; mo, month; NSC, neuropathy symptom and change; QoL-DN, Quality of Life–Diabetic Neuropathy; SD, standard deviation; SF-36 PCS, 36-Item Short Form Survey physical component summary.

eTable 3. Week 35 efficacy outcomes from NEURO-TTRansform (eplontersen and inotersen reference groups) and NEURO-TTR[1] (inotersen and placebo groups).

	NEURO-TTRansform		NEURO-TTR	
	Eplontersen (N = 141)	**Inotersen (reference) (N = 21)**	**Inotersen (N = 106)**	**Placebo[a] (N = 59)**
Serum transthyretin concentration, *n*	*139*	*20*	*94*	*57*
Percent change from baseline, mean (SD)	–82.1 (11.7)	–74.26 (23.3)	–79.27 (12.8)	–11.13 (19.6)
Median (Q1, Q3)	–84.4 (–90.2, –77.5)	–82.1 (–91.5, –67.5)	–83.6 (–87.9, –72.7)	–9.5 (–25.7, –0.6)
mNIS+7 composite score[b], *n*	*138*	*19*	*95*	*55*
Change from baseline, mean (SD)	–0.04 (16.2)	4.06 (13.4)	1.45 (14.4)	9.76 (14.2)
Median (Q1, Q3)	–0.09 (–6.3, 7.7)	2.9 (–5.2, 10.5)	0.2 (–6.1, 10.7)	9.5 (–2.1, 19.3)
Norfolk QoL-DN total score[c], *n*	*130*	*20*	*94*	*57*
Change from baseline, mean (SD)	–4.8 (16.5)	–3.0 (12.1)	–0.3 (16.59)	5.5 (20.2)
Median (Q1, Q3)	–2.5 (–13.0, 2.0)	–3.0 (–6.0, 2.5)	–2.0 (–12.0, 11.0)	5.0 (–8.0, 17.0)

[a]Historical placebo in NEURO-TTRansform.

[b]Composite scores on the mNIS+7 scale range from −22.3 to 346.3, with higher scores indicating poorer function.

[c]Total scores on the Norfolk QoL-DN questionnaire range from −4 to 136, with higher scores indicating poorer quality of life. Q1, Q3 represent first and third quartiles.

mNIS+7, modified Neuropathy Impairment Score+7; QoL-DN, Quality of Life–Diabetic Neuropathy.

eTable 4. Interim analysis results at week 35.

	Eplontersen (N = 140)	**Historical Placebo (N = 59)**	**Difference (95% CI)**
Primary endpoints			
Serum transthyretin Concentration,			
n	136	57	
Adjusted percentage Change from baseline	–81.2	–14.8	–66.4
95% CI	–84.6 to –77.8	–18.7 to –10.8	–71.4 to –61.5
P value			< .001
mNIS+7 composite score, n	140	59	
Adjusted change from baseline	0.22	9.22	–9.01
95% CI	–3.5 to 3.9	5.5 to 12.9	–13.5 to –4.5
P value			< .001
Secondary endpoint			
Norfolk QoL-DN total score, n	133	58	
Adjusted change from baseline	–3.1	8.7	–11.8
95% CI	–7.2 to 1.0	4.5 to 12.8	–16.8 to –6.8
P value			< .001

[a]Interim Analysis Methodology.

A prespecified interim analysis was performed when all patients in NEURO-TTRansform had completed the week 35 assessments. The efficacy analysis population included all enrolled patients who received at least 1 dose of trial medication and who had a baseline and at least 1 post-baseline mNIS+7 or Norfolk QoL-DN assessment. The interim analysis compared primary and secondary endpoints between the eplontersen treatment group at week 35 and the placebo arm of the NEURO-TTR trial[1] at week 35.

Prespecified primary endpoints of the interim analysis included percent change from baseline to week 35 in serum transthyretin concentration and change from baseline to week 35 in mNIS+7 composite score. The secondary endpoint for the interim analysis was change from baseline to week 35 in the Norfolk QoL-DN total score.

- Transthyretin: The percentage change in serum transthyretin from baseline to week 35 was analyzed using the MMRM model adjusted by propensity score weights. The MMRM model included the effects of treatment (eplontersen or historical placebo), time (categorical), disease stage (stage 1/stage 2), V30M variant (yes/no), and previous treatment with tafamidis or diflunisal (yes/no), treatment × time interaction, baseline value of the endpoint, and the baseline × time interaction. The propensity score was calculated for each historical placebo or eplontersen patient using a logistic regression model with covariates including disease stage (stage 1/stage 2), V30M variant (yes/no), and previous treatment with tafamidis or diflunisal (yes/no).
- mNIS+7 composite score: Because only 1 post-baseline assessment (week 35) was available at the week 35 interim analysis, the treatment comparison at week 35 was based on the ANCOVA model adjusted by propensity score. The ANCOVA model included the effects of treatment (eplontersen or historical placebo), disease stage (stage 1/stage 2), V30M variant (yes/no), previous treatment with tafamidis or diflunisal (yes/no), and the baseline value of the endpoint. Patients with a missing mNIS+7 composite score at week 35 had values multiple imputed using an imputation model (based on MAR assumption) that contained the following variables: disease stage (stage 1/stage 2), V30M variant (yes/no), previous treatment with tafamidis or diflunisal (yes/no), and the baseline value of the endpoint, and the multiple imputation was stratified by treatment group.[6,7]
- Norfolk QoL-DN total score: If both primary endpoints of the interim analysis (serum transthyretin concentration and mNIS+7 composite score) were significant at alpha level of 2-sided 0.025, then the secondary endpoint (Norfolk QoL-DN total score) was to be tested at the interim analysis at alpha level of 0.025 (comparison of change from baseline to week 35 in the Norfolk QoL-DN total score between eplontersen and historical placebo). Because only 1 post-baseline Norfolk QoL-DN assessment (week 35) was available for the interim analysis, the same analysis methodology described for mNIS+7 composite score was applied for the Norfolk QoL-DN analysis.

ANCOVA, analysis of covariance; MAR, missing at random; MMRM, mixed-effects model with repeated measures; mNIS+7, modified Neuropathy Impairment Score+7; QoL-DN, Quality of Life–Diabetic Neuropathy.

eTable 5. Treatment-emergent adverse events through week 66[a] with an incidence ≥ 10% in any group by preferred term.

Preferred Term	Eplontersen (N = 144)	Historical Placebo (N = 60)
COVID-19	35 (24)	NA
Diarrhea	24 (17)	11 (18)
Urinary tract infection	24 (17)	10 (17)
Vitamin A deficiency[b]	17 (12)	NR
Nausea	16 (11)	7 (12)
Dizziness	10 (7)	6 (10)
Headache	9 (6)	7 (12)
Pain in extremity	9 (6)	8 (13)
Nasopharyngitis	8 (6)	6 (10)
Fall	8 (6)	13 (22)
Fatigue	7 (5)	12 (20)
Cough	7 (5)	8 (13)
Thermal burn	6 (4)	6 (10)
Constipation	4 (3)	6 (10)
Neuralgia	4 (3)	9 (15)
Asthenia	3 (2)	8 (13)
Hypoaesthesia	2 (1)	6 (10)
Pain	1 (1)	8 (13)
Muscular weakness	1 (1)	6 (10)

Data are No. (%).

[a]Data through week 85 are presented in eTable 7.

[b]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.

NA, not applicable; NR, not reportable.

eTable 6. Key endpoint analysis datapoints by study visit.

	Eplontersen (N = 141)	**Historical Placebo (N = 59)**	**Adjusted Mean Difference (95% CI) *P* value**
Serum transthyretin concentration percent change from baseline			
Week 5	*n = 132*	*n = 58*	NA
Mean	–51.8	–4.8	
Median (Q1, Q3)	–51.5 (–64.9, –39.6)	–11.3 (–22.3, 0.0)	
Week 8[a]/9[b]	*n = 136*	*n = 59*	NA
Mean	–66.4	–6.4	
Median (Q1, Q3)	–67.8 (–79.6, –54.5)	–8.7 (–19.4, 1.5)	
Week 13	*n = 136*	*n = 59*	NA
Mean	–73.2	–10.2	
Median (Q1, Q3)	–74.3 (–84.2, –63.7)	–9.8 (–24.8, 0.8)	
Week 23[a]/25[b]	*n = 140*	*n = 55*	NA
Mean	–79.3	–12.0	
Median (Q1, Q3)	–82.7 (–88.4, –73.0)	–10.0 (–26.9, 2.9)	
Week 35	*n = 139*	*n = 57*	NA
Mean	–82.1	–11.1	
Median (Q1, Q3)	–84.4 (–90.2, –77.5)	–9.5 (–25.7, –0.6)	
Week 47[a]/49[b]	*n = 136*	*n = 53*	NA
Mean	–81.9	–6.4	
Median (Q1, Q3)	–84.7 (–90.1, –75.5)	–10.8 (–22.9, 6.4)	
Week 59[a]/57[b]	*n = 135*	*n = 50*	NA
Mean	–81.5	–6.8	
Median (Q1, Q3)	–83.6 (–90.3, –75.5)	–10.8 (–19.8, 4.8)	

Week 65	*n = 135*	*n = 51*	NA
Mean	–83.0	–6.0	
Median (Q1, Q3)	–85.0 (–91.7, –76.0)	–7.4 (–19.4, 6.4)	
Week 85[c]	*n = 129*		
Mean	–81.8	NA	NA
Median (Q1, Q3)	–86.2 (–90.8, –-75.9)		
mNIS+7 composite score change from baseline			
Week 35	*n = 138*	*n = 55*	
Adjusted mean (95% CI)	0.7 (–3.1 to 4.5)	10.0 (6.3 to 13.8)	–9.35 (–13.9 to –4.8) P < .001
Mean	–0.04	9.8	NA
Median (Q1, Q3)	–0.1 (–6.3 to 7.7)	9.9 (–2.1 to 19.3)	NA
Week 66	*n = 128*	*n = 52*	
Adjusted mean (95% CI)	0.3 (–4.5 to 5.1)	25.1 (20.2 to 29.9)	–24.8 (–31.0 to –18.6) P < .001
Mean	-0.2	23.9	NA
Median (Q1, Q3)	–1.1 (–10.2 to 10.6)	24.7 (4.4 to 38.1)	NA
Week 85	*n = 122*	NA	NA
Adjusted mean (95% CI)	NA		
Mean	–2.9	NA	NA
Median (Q1, Q3)	–1.9 (–11.3 to 8.3)	NA	NA
Norfolk QoL-DN total score change from baseline			
Week 35	*n = 130*	*n = 57*	
Adjusted mean (95% CI)	–3.6 (–7.7 to 0.5)	8.2 (4.0 to 12.4)	–11.8

			(–16.9 to –6.8) P <.001
Mean	–4.8	5.5	NA
Median (Q1, Q3)	–2.5 (–13.0 to 2.0)	5.0 (–8.0 to 17.0)	NA
Week 66	*n = 128*	*n = 52*	
Adjusted mean (95%CI)	–5.5 (–10.0 to –1.0)	14.2 (9.5 to 19.0)	–19.7 (–25.6 to –13.8) P < .001
Mean	–7.2	10.8	NA
Median (Q1, Q3)	–5.0 (–17.0 to 4.0)	11.0 (0.0 to 23.7)	NA
Week 85	*n = 119*	NA	NA
Adjusted mean (95% CI)	NA	NA	NA
Mean	–6.2	NA	NA
Median (Q1, Q3)	–5.0 (–15.3 to 5.0)	NA	NA

[a]Placebo (NEURO-TTR time point).

[b]Eplontersen (NEURO-TTRansform time point).

[c]Data from nominal visit at week 85.

Ns are numbers of patients with nonmissing data at the time point.

mNIS+7, modified Neuropathy Impairment Score+7; NA, not applicable; QoL-DN, Quality of Life–Diabetic Neuropathy.

eTable 7. Secondary analysis datapoints by study visit (source data for Figures 3A, 3B, and 3D).

	Eplontersen (N = 141)	**Historical Placebo (N = 59)**	**Adjusted Mean Difference (95% CI) *P* value**
NSC total score, change from baseline, adjusted mean (95% CI)			
Week 35	*n = 141* 0.8 (–0.9 to 2.5)	*n = 56* 4.7 (3.0 to 6.6)	–3.94 (–6.1 to –1.8) *P* < .001
Week 66	*n = 132* –0.03 (–1.9 to 1.9)	*n = 52* 8.2 (6.2 to 10.1)	–8.2 (–10.7 to –5.8) *P* < .001
SF-36 PCS, change from baseline, adjusted mean (95% CI)			
Week 35	*n = 140* 0.5 (–0.9 to 1.8)	*n = 57* –1.7 (–3.1 to –0.3)	2.2 (0.5 to 3.9) *P* < .05
Week 65	*n = 136* 0.9 (–0.7 to 2.4)	*n = 50* –4.5 (–6.1 to –2.8)	5.3 (3.2 to 7.4) *P* < .001
mBMI, $kg/m^2 \times g/L$ change from baseline			
Week 13	*n = 120*	*n = 59*	
Adjusted mean (95% CI)	–17.2 (–34.7 to 0.4)	5.1 (–12.3 to 22.4)	–22.2 (–44.3 to –0.1) P = 0.05

Mean	–12.7	6.4	NA
Median (Q1, Q3)	–8.9 (–53.3 to 31.3)	0.0 (–44.4 to 37.7)	NA
Week 35	*n = 131*	*n = 57*	33.8
Adjusted mean (95% CI)	–17.7 (–35.8 to 0.4)	–51.5 (–69.9 to –33.1)	(10.4 to 57.2)
			P < .01
Mean	–13.0	–49.5	NA
Median (Q1, Q3)	–5.0 (–65.6 to 37.3)	–50.1 (–107.5 to 12.2)	NA
Week 65	*n = 130*	*n = 49*	82.7
Adjusted mean (95% CI)	–8.1 (–28.6 to 12.4)	–90.8 (–112.8 to –68.7)	(54.6 to 110.8)
			P < .001
Mean	–4.6	–85.2	NA
Median (Q1, Q3)	3.3 (–63.4 to 47.4)	–73.0 (–159.2 to –22.4)	NA
Week 85	*n=72*	NA	NA
Adjusted mean (95% CI)	NA	NA	NA
Mean	–9.7	NA	NA
Median (Q1, Q3)	–20.8 (–63.2 to 41.9)	NA	NA

Ns are numbers of patients with nonmissing data at the time point.

mBMI, modified body mass index; NSC, neuropathy symptom and change; SF-36 PCS, 36-Item Short Form Survey physical component summary.

eTable 8. Summary of treatment-emergent adverse eventsthrough end of treatment (week 85+)

Events	Eplontersen (N = 144)
Any TEAE	141 (98)
Leading to study drug discontinuation[b]	8 (6)
Maximum severity of TEAEs	
Mild	64 (44)
Moderate	57 (40)
Severe	20 (14)
Adverse events of special interest[c]	43 (30)
Ocular events potentially related to vitamin A deficiency	41 (29)
Vitamin A deficiency/decreased/abnormal	23 (16)
Ocular events potentially related to vitamin A deficiency (excluding vitamin A deficiency/decreased/abnormal)	26 (18)
Thrombocytopenia	3 (2)
Glomerulonephritis	0
Leading to study drug discontinuation	0
Injection site reactions[d]	13 (9)
Flu-like symptoms[e]	1 (1)
Abnormal liver function[f]	11 (8)
Any serious TEAE	27 (19)
Related to study drug	0
Death	3 (2)[g]
Death due to study drug	0

[a]Shown are TEAEs, defined as adverse events that first occurred, or worsened, after the first dose of study drug. Includes all safety data collected through April 7, 2023, including data after week 85.

[b]1-fatal cardiac arrhythmia, 1-acute myocardial infarction, 1-fatal intracerebral hemorrhage, 1-urosepsis, 1-proteinuria, 1-renal impairment, 1-transaminases abnormal, 1-malignant lung neoplasm.

[c]Definitions of Adverse Events of Special Interest are provided in eTable 8.

[d]Injection site reactions were defined as TEAEs with preferred terms containing the text “Injection site.”

[e]Flu-like symptoms were defined as TEAEs with the preferred term Influenza like illness; or the preferred term pyrexia (or feeling hot or body temperature increased) plus at least 1 of the following symptoms: chills, myalgia, arthralgia, malaise, fatigue, headache, nausea.

[f]TEAE within the Standardized MedDRA Query: drug-related hepatic disorders–comprehensive search.

[g]The 3 deaths were consistent with known sequelae of ATTRv: 1 patient with known ATTRv cardiomyopathy experienced a fatal cardiac arrhythmia after receiving 4 doses of eplontersen; 1 patient died from intracerebral hemorrhage after receiving 10 doses of eplontersen (platelet counts and coagulation parameters were normal); 1 patient with known ATTRv cardiomyopathy experienced a fatal myocardial infarction after receiving 19 doses of eplontersen. After the week 85 analysis was completed, an additional patient was confirmed to have died before the week 85 analysis cutoff. This patient died 103 weeks after enrollment in the study (study day 726). The patient discontinued treatment 64 weeks (study day 272) prior to their death, having received 5 doses of eplontersen, and elected for survival follow-up before their death from pneumonia sepsis.

Data are No. (%).

ATTRv, hereditary transthyretin; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

eTable 9. Cumulative treatment-emergent adverse events through end of treatment (week 85+) with an incidence ≥ 10% by preferred term.

Preferred Term	Eplontersen (N = 144)
COVID-19	48 (33)
Diarrhea	28 (19)
Urinary tract infection	28 (19)
Vitamin A deficiency	17 (12)
Nausea	16 (11)

Data are No. (%).

[a]Includes all safety data collected through April 7, 2023, including data after week 85.

eTable 10. Definitions of adverse events of special interest.

Adverse Event of Special Interest	Definition
Thrombocytopenia	PT: Thrombocytopenia; Platelet count decreased
Glomerulonephritis	PT: Nephritis; Glomerulonephritis; Glomerulonephritis proliferative; Glomerulonephritis acute; Glomerulonephritis rapidly progressive; C3 Glomerulonephritis; Chronic autoimmune glomerulonephritis; Glomerulonephritis chronic; Fibrillary glomerulonephritis; Glomerulonephritis membranoproliferative; Glomerulonephritis membranous; Glomerulonephritis minimal lesion; Henoch-Schonlein purpura nephritis; Immune mediated nephritis; Immunotactoid glomerulonephritis; Lupus nephritis; Nephritis allergic; Nephrotic syndrome
Ocular events potentially related to vitamin A deficiency	PT: Vitamin A decreased; Vitamin A abnormal HLT: Fat soluble vitamin deficiencies and disorders SMQ: Optic nerve disorders; Corneal disorders; Retinal disorders

HLT, high-level term; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, standardized MedDRA query.

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