Received: 1 November 2021 | Revised: 29 June 2022 | Accepted: 30 June 2022

DOI: 10.1002/mus.27675

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Long-term treatment effects of inotersen on health-related quality of life in patients with hATTR amyloidosis with polyneuropathy: Analysis of the open-label extension of the NEURO-TTR trial

Chafic Karam MD[1] | Duncan Brown PhD[2] | Min Yang MD, PhD[3] | Nicolae Done PhD[3] | Jing Jing Zhu BA[3a] | Alexandra Greatsinger MA[3] | Ana Bozas PhD, CMPP[2a] | Montserrat Vera-Llonch MD, MPH[2] | James Signorovitch PhD[3]

[1]Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

[2]Ionis Pharmaceuticals/Akcea Therapeutics, Inc, Boston, Massachusetts

[3]Analysis Group, Inc, Boston, Massachusetts

Correspondence
Duncan Brown, Ionis Pharmaceuticals/Akcea Therapeutics, 22 Boston Wharf Road, 9th Floor, Boston, MA 02210.
Email: dbrown@akceatx.com

Funding information
Ionis Pharmaceuticals/Akcea Therapeutics, Inc.

Abstract

Introduction/Aims: Hereditary transthyretin-mediated amyloidosis with polyneuropathy (hATTR-PN) progressively affects patients' functionality and compromises health-related quality of life (HRQL). The aim of this study was to quantify the projected long-term treatment effects of inotersen vs placebo on HRQL measures.

Methods: The inotersen phase 2/3 randomized, double-blind, placebo-controlled trial NEURO-TTR (NCT01737398, 65 weeks) and its subsequent open-label extension (OLE; NCT02175004, 104 weeks) included 172 (112 inotersen and 60 placebo) patients. Placebo double-blind period and overall inotersen-inotersen (double-blind/OLE) treatment period (170 weeks) data were used to extrapolate the long-term placebo-placebo effect using mixed-effects models with repeated measures. Changes from baseline in the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) and 36-Item Short Form Health Survey version 2 (SF-36v2) in hATTR-PN were estimated. Differences in changes were compared between the inotersen-inotersen and extrapolated placebo-placebo arms.

Results: Inotersen-inotersen patients maintained their HRQL with an observed change ranging from 10.3% improvement (Norfolk QoL-DN item "Pain kept you awake at night") to 11.6% deterioration (SF-36v2 Activities of Daily Living subdomain). The extrapolated placebo-placebo results suggest greater deterioration over time compared with inotersen-inotersen treatment on Norfolk QoL-DN total score (23.6; 95% confidence interval [CI], 8.9-38.3; $P < .01$), Activities of Daily Living (4.6; 95% CI, 2.0-7.3; $P < .001$), and "Pain kept you awake at night" (1.2; 95% CI, 0.4-1.9; $P < .01$). Similarly, greater deterioration was expected for the SF-36v2 Physical

Abbreviations: ADL, activities of daily living; AN, autonomic neuropathy; BP, bodily pain; CI, confidence interval; FDA, US Food and Drug Administration; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; HRQL, health-related quality of life; GH, General Health; LFN, large-fiber neuropathy; LLF, lower limb function; MMRM, mixed-effects models with repeated measures; mNIS+7, modified Neuropathy Impairment Score+7; NSC, Neuropathy Symptom and Change; OLE, open-label extension; PCS, Physical Component Summary; PF, physical functioning; QoL-DN, Quality of Life-Diabetic Neuropathy; RE, Role-Emotional; RP, Role-Physical; S, symptoms; SD, standard deviation; SE, standard error; SF-36v2, 36-item Short Form Health Survey version 2; SFN, small-fiber neuropathy; TTR, transthyretin.

[a] Affiliation at the time the study was conducted.

Component Summary (8.0; 95% CI, 3.2-12.8, $P < .01$), Bodily Pain (7.8; 95% CI, 2.0-13.5; $P < .01$), and Physical Functioning (10.6; 95% CI, 5.5-15.6; $P < .0001$).

Discussion: Long-term (>3 years) inotersen treatment was associated with slowing and, in some domains, halting of deterioration in key HRQL outcome measures, particularly physical functioning and pain.

KEYWORDS

amyloidosis, inotersen, neuropathic pain, Norfolk Quality of Life---Diabetic Neuropathy, physical functioning, quality of life, 36-item Short-Form Health Survey, transthyretin

1 | INTRODUCTION

Hereditary transthyretin amyloidosis (hATTR) is a progressive, multisystemic disease caused by the misfolding of the transthyretin protein (TTR) due to genetic mutations in its encoding gene.[1] The characteristic accumulation of deposited TTR in multiple organs ultimately results in impaired physical, mental, and social functioning; compromised health-related quality of life (HRQL); and reduced life expectancy.[1–7] hATTR has also been shown to severely impact work productivity and the ability to carry out activities of daily living (ADL).[3,5,8,9] One of the main clinical manifestations of the disease is progressive polyneuropathy (hATTR-PN).[1,10,11] More than 150 different mutations responsible for hATTR-PN have been identified, with the most common being the Val30Met mutation (148G→A).[1]

Studies have documented the significant disease burden experienced by patients with hATTR and the way in which it impacts their HRQL, with consequences on self-reported physical health, pain/discomfort, mobility, and ability to perform usual activities being particularly pronounced.[5,7,11] A clear relationship was established between the increasing duration of symptoms of patients with hATTR-PN and worsening scores on measures of HRQL, such as the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire.[12,13]

A promising novel agent, inotersen, is an antisense oligodeoxynucleotide that was designed to inhibit TTR production by binding to its messenger RNA.[14,15] In its randomized, double-blind, placebo-controlled phase III trial, NEURO-TTR (NCT01737398), inotersen was shown to be significantly more effective than placebo in delaying hATTR-PN progression in terms of the course of neurological disease and HRQL.[16] Consequently, inotersen was first approved by the US Food and Drug Administration (FDA) for the treatment of hATTR-PN in 2018.[17]

Recently, results from the NEURO-TTR open-label extension (OLE) study, whereby 135 patients were followed for up to 104 weeks, became available, and showed an immediate drop of serum TTR levels after initiating inotersen among patients who had previously received placebo in the NEURO-TTR study.[18] Given the marked impacts of hATTR-PN on pain and physical functioning, and evidence of worse HRQL among patients with hATTR compared with other diseases,[3] HRQL is considered a key objective in disease management and is often used as a surrogate endpoint in trials investigating TTR stabilizers or RNA interference drugs.[19] A descriptive study conducted using interim OLE data assessed the changes in HRQL and reported that the scores remained stable from OLE baseline to week 104, suggesting that long-term treatment with inotersen can preserve HRQL in patients with hATTR-PN.[20] However, the results were descriptive in nature, limiting direct, longitudinal comparisons between treatment arms, which is key when assessing the effects of inotersen on HRQL and functional domains that indicate halting or slowing of disease progression.[3,21] Toward that end, our aim in the current study was to use data from the NEURO-TTR and OLE to describe the long-term treatment effects of inotersen on HRQL measures as well as specific domains measuring physical pain and functioning. Importantly, we sought to statistically compare these outcomes with those expected without treatment if trends in HRQL observed in the placebo arm during the NEURO-TTR double-blind period were to continue in the longer term.

2 | METHODS

2.1 | Data sources and study population

The NEURO-TTR was a multicenter, double-blind, phase III trial of patients with hATTR-PN who were randomly assigned to receive inotersen or placebo at a ratio of 2:1 over 65 weeks (Figure S1). Patients were required to have a Neuropathy Impairment Score+7 (NIS+7) between 10 and 130, a *TTR* mutation determined by genotyping, and documented amyloid deposits determined via biopsy. Other inclusion and exclusion criteria have been documented elsewhere.[16] The three randomization strata included Val30Met TTR mutation status (yes or no), disease stage (ie, stage 1 [no ambulatory assistance required] or stage 2 [assistance with ambulation required]),[22] and previous treatment status (tafamidis/diflunisal or none). Patients assigned placebo or inotersen in the NEURO-TTR trial received inotersen in the OLE study and constituted the placebo-inotersen and inotersen-inotersen arms, respectively (Figure S1). The trial protocols for NEURO-TTR and the OLE were approved by the relevant institutional review boards or local ethics committees and regulatory authorities. All patients provided written informed consent to participate in the NEURO-TTR and the OLE.

2.2 | Outcome measures

The outcomes of this post-hoc analysis were the composite, domain, and select item scores of the Norfolk QoL-DN and the 36-item Short Form Health Survey version 2 (SF-36v2) Physical Component Summary (PCS). In the NEURO-TTR trial, outcome data were captured at baseline, week 35, and week 66 (week 65 for SF-36v2); in the OLE period, data on the measures were captured at weeks 26, 52, 78, and 104. Although domain and item scores were comprehensively analyzed for Norfolk QoL-DN and SF-36v2 PCS, impacts on scores related to pain and physical functioning, respectively, were highlighted and grouped together across both HRQL instruments to emphasize any patterns in the effects of inotersen across these domains. Detailed definitions and score ranges for Norfolk QoL-DN and the SF-36v2 PCS domains and items are shown in Table S1.

2.2.1 | Norfolk QoL-DN

The Norfolk QoL-DN is a 35-item patient self-reporting questionnaire that captures symptoms of peripheral and autonomic neuropathy[23] and has been validated in patients with hATTR-PN.[13] It consists of a HRQL composite score (a primary endpoint in the NEURO-TTR trial and a secondary endpoint in the OLE study) ranging from −4 to 136, whereby higher scores indicate worse HRQL. The total score (serving as a tertiary endpoint in the NEURO-TTR trial) consists of the summation of the following 5 subdomain scores: Physical Functioning/Large Fiber Neuropathy (PF/LFN), Activities of Daily Living (ADL), Symptoms (S), Small-Fiber Neuropathy (SFN), and Autonomic Neuropathy (AN).

Specific items of interest for this study were those measuring the presence of pain, ranging from 0 ("not a problem") to 4 ("severe problem"), including "superficial pain," "deep pain," "pain that kept you awake at night," and "pain that interferes with normal work," as described in full detail in Table S1.

2.2.2 | SF-36v2 PCS

The SF-36v2 questionnaire assesses generic HRQL using a 36-item patient-reported outcome measure of functional health and well-being,[24] and has been used in trials comparing disease progression and HRQL in patients with hATTR-PN.[25] The items are aggregated by eight domains of functional health and well-being, and further summarized by two composite scores: the PCS and the Mental Component Summary score. The PCS has norm-based scoring with a population mean of 50 and standard deviation of 10, and consists of the following domain scores: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), and General Health (GH). These domains were analyzed in this study. The Mental Component Summary score includes Vitality, Social Functioning, Role-Emotional (RE), and Mental Health domains, and was not included in the analyses because the focus of the NEURO-TTR trial was on the impact of inotersen on the SF-36v2 physical scores.

2.3 | Statistical analyses

Baseline characteristics, including demographics, randomization strata, and disease characteristics, were summarized for all patients included in the full analysis set, both overall and separately for the inotersen-inotersen and placebo-inotersen study cohorts. Means and standard deviations are reported for continuous variables and counts and percentages are reported for categorical variables. Statistical comparisons between the placebo-inotersen and inotersen-inotersen groups were conducted using one-way analysis of variance for continuous variables and the chi-square test for categorical variables.

Data from the NEURO-TTR double-blind period for patients receiving the placebo were used to extrapolate the predicted outcome values during the OLE period by continuing trends observed during the placebo period using mixed-effects models with repeated measures (MMRM; as described further in the Statistical Analysis section of Appendix S1).

The MMRM-predicted values for the placebo-inotersen group during the OLE period can be interpreted as estimated counterfactuals for the outcome values observed for patients in the placebo group had they not been treated with inotersen during the OLE period. To estimate the long-term effect of treatment with inotersen, the extrapolated outcome values were compared between patients receiving placebo or inotersen over the NEURO-TTR trial + OLE period (ie, at 35, 65/66, 92, 118, 144, and 170 weeks from the initiation of the double-blind NEURO-TTR period) using the MMRM's least-squares mean change from baseline.

The difference in mean change between the MMRM-predicted values for the inotersen arm and the MMRM-extrapolated values for the placebo arm from the baseline period were reported at key timepoints. Standard errors (SEs), 95% confidence intervals (CIs), and *P* values were reported for mean differences. Notably, these methods differ from those in previously published analyses, which did not use mixed- models for predictions and instead relied on calculating the best linear fit for each outcome measure and extrapolating the equation to week 104 of the OLE study period.[7] The mixed-model approach allows for a more accurate prediction of outcomes during the OLE period using patient covariates and allowing for more flexibility across patient trajectories over time.

3 | RESULTS

3.1 | Study sample

A total of 172 randomized patients received at least one dose of the trial regimen, with 112 in the inotersen-inotersen group and 60 in the placebo-inotersen group. Among these, 165 patients had baseline values measured and at least one post-baseline efficacy assessment

for the mNIS+7 test composite score or Norfolk QoL-DN total score, and thus comprised the full analysis set. Complete details on patient enrollment are available for the NEURO-TTR trial and OLE.[16,18]

3.2 | Baseline characteristics

The baseline demographics and disease characteristics were generally well-balanced between the inotersen-inotersen and placebo-inotersen groups (Table 1). The Norfolk QoL-DN scores, as reported in previous work,[18] were also comparable between the inotersen-inotersen and placebo-inotersen groups at OLE screening, although inotersen-inotersen patients had higher rates of previous use of stabilizers and cardiomyopathy. Results for pharmacodynamics outcome (ie, change in serum TTR levels) and for safety and tolerability of inotersen during the OLE period have been reported elsewhere.[18]

3.3 | Study outcomes

3.3.1 | Norfolk QoL-DN total score

The extrapolated mean changes from baseline to week 170 (ie, week 104 of OLE) for Norfolk QoL-DN total scores,

TABLE 1 Baseline demographics and disease characteristics of patients in the NEURO-TTR full analysis set

	All patients (N = 165)	Inotersen-inotersen arm (n = 106)	Placebo-inotersen arm (n = 59)	*P* value
Age (years), mean ± SD	59.5 ± 13.0	59.6 ± 12.4	59.4 ± 14.1	0.94
Male, n (%)	116 (70.3%)	75 (70.8%)	41 (69.5%)	>0.99
White, n (%)	152 (92.1%)	100 (94.3%)	52 (88.1%)	0.08
Region, n (%)				0.76
North America	79 (47.9%)	53 (50.0%)	26 (44.1%)	
Europe	57 (34.6%)	35 (33.0%)	22 (37.3%)	
Other	29 (17.6%)	18 (17.0%)	11 (18.6%)	
BMI (kg/m^2), mean ± SD	24.3 ± 4.8	24.3 ± 4.8	24.3 ± 4.9	0.98
Val30Met TTR mutation, n (%)	87 (52.7%)	54 (50.9%)	33 (55.9%)	0.65
Disease stage, n (%)				0.70
Stage 1	113 (68.5%)	71 (67.0%)	42 (71.2%)	
Stage 2	52 (31.5%)	35 (33.0%)	17 (28.8%)	
Previous treatment with tafamidis or diflunisal, n (%)	97 (58.8%)	62 (58.5%)	35 (59.3%)	>0.99
hATTR-PN, mean ± SD				
Duration of disease from diagnosis (months)	42.1 ± 48.3	43.5 ± 52.3	39.8 ± 40.5	0.64
Duration from symptom onset (months)	64.8 ± 53.6	65.0 ± 54.4	64.4 ± 52.7	0.95
PND score, n (%)				0.67
1	54 (32.7%)	31 (29.3%)	23 (39.0%)	
2	59 (35.8%)	40 (37.7%)	19 (32.2%)	
3	43 (26.1%)	29 (27.4%)	14 (23.7%)	
4	9 (5.5%)	6 (5.7%)	3 (5.1%)	
hATTR-CM, n (%)	65 (39.4%)	43 (40.6%)	22 (37.3%)	0.81
hATTR-CM, mean ± SD				
Duration of disease from diagnosis (months)	23.6 ± 26.7	25.0 ± 28.8	21.0 ± 22.5	0.57
Duration from symptom onset (months)	41.4 ± 50.8	45.4 ± 59.2	34.1 ± 29.3	0.45
NT-proBNP (pmol/L), mean ± SD	105.4 ± 228.8	118.8 ± 260.1	82.2 ± 160.5	0.33
NYHA score, n (%)				0.76
I	108 (65.5%)	68 (64.2%)	40 (67.8%)	
II	57 (34.6%)	38 (35.9%)	19 (32.2%)	
Karnofsky performance status score, mean ± SD	76.8 ± 11.0	76.7 ± 11.1	77.0 ± 10.9	0.87

Abbreviations: BMI, body mass index; hATTR-CM/PN, hereditary transthyretin amyloidosis–cardiomyopathy/polyneuropathy; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; SD, standard deviation; TTR, transthyretin.

subdomain scores, and key pain-related items are shown in Figure 1 (raw mean changes and SEs are shown in Figure **S2**). After 170 weeks, the extrapolated Norfolk QoL-DN total score for patients in the placebo-inotersen group indicated significantly greater deterioration relative to the inotersen-inotersen group.

The extrapolated difference in the total Norfolk QoL-DN scores between the MMRM-predicted inotersen arm and the MMRM-extrapolated placebo arm was statistically significant at all follow-up time-points of interest (Figure **S3**).

3.3.2 | SF-36v2 PCS

Changes from baseline to week 170 in the mean SF-36v2 PCS score and subdomain scores are shown in Figure 2. After 170 weeks, patients in the placebo-inotersen arm had worse extrapolated HRQL with a mean MMRM-predicted decrease in SF-36v2 PCS score of 8.65 (SE, 2.22) relative to 0.66 (SE, 1.03) in the inotersen-inotersen arm.

The extrapolated difference in scores between the MMRM-predicted inotersen arm and the MMRM-extrapolated placebo arm was statistically significant at all follow-up time-points of interest (Figure **S4**).

3.3.3 | Pain-related outcomes

The Norfolk QoL-DN Superficial Pain item is presented in Figure 3A. The difference between the MMRM-predicted inotersen arm and the MMRM-extrapolated placebo arm favored inotersen, and was statistically significant at weeks 66, 92, and 118, but not thereafter.

The Norfolk QoL-DN Deep Pain item is presented in Figure 3B. Similarly, the difference in scores between the MMRM-predicted

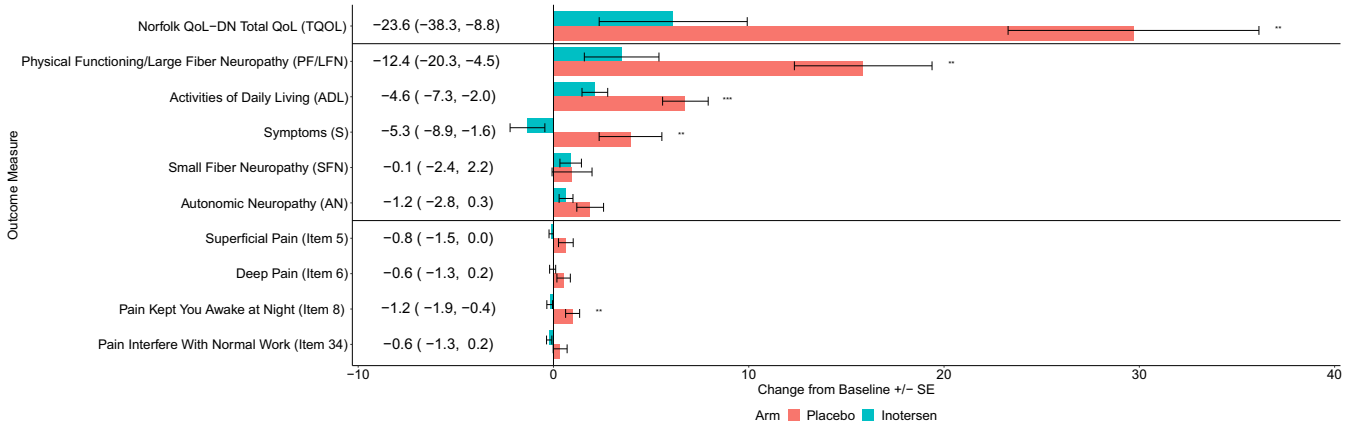

FIGURE 1 Comparison of extrapolated changes in mean Norfolk QoL-DN scores from baseline to week 170 (week 104 of OLE) in the inotersen and placebo arms, and mean treatment differences (inotersen minus placebo). Statistically significant nonzero differences between treatment arms are noted: *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001. The 95% confidence intervals for treatment differences are shown in parentheses. Higher scores indicate worse QoL; negative mean differences indicate better outcomes for the inotersen arm. Abbreviations: OLE, open-label extension; QoL-DN, Quality of Life–Diabetic Neuropathy.

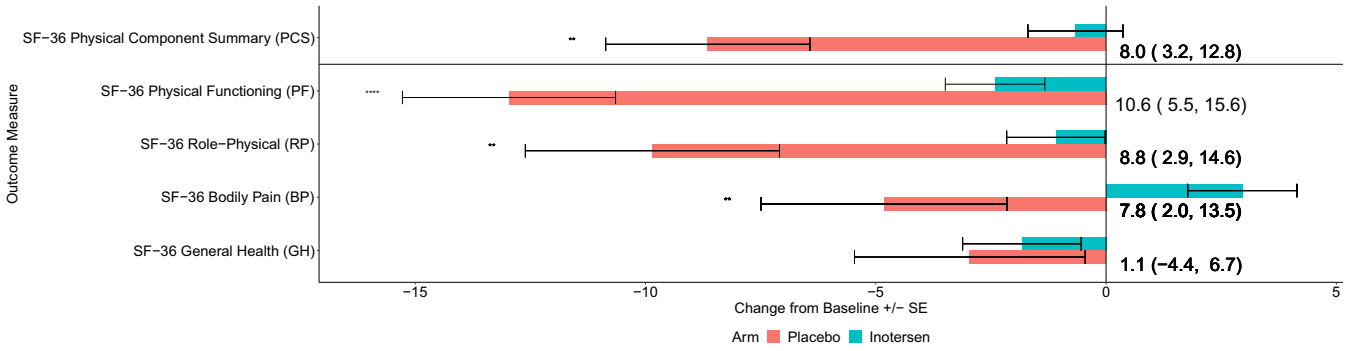

FIGURE 2 Comparison of extrapolated changes in mean 36-item Short Form Health Survey version 2 Physical Component Summary score and subdomain subscores from baseline to week 170 (week 104 of OLE) in the inotersen and placebo arms, and mean treatment differences (inotersen minus placebo). Statistically significant nonzero differences between treatment arms are noted: *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001. The 95% confidence intervals for treatment differences are shown in parentheses. Higher scores indicate better quality of life; negative mean differences indicate better outcomes for the inotersen arm.

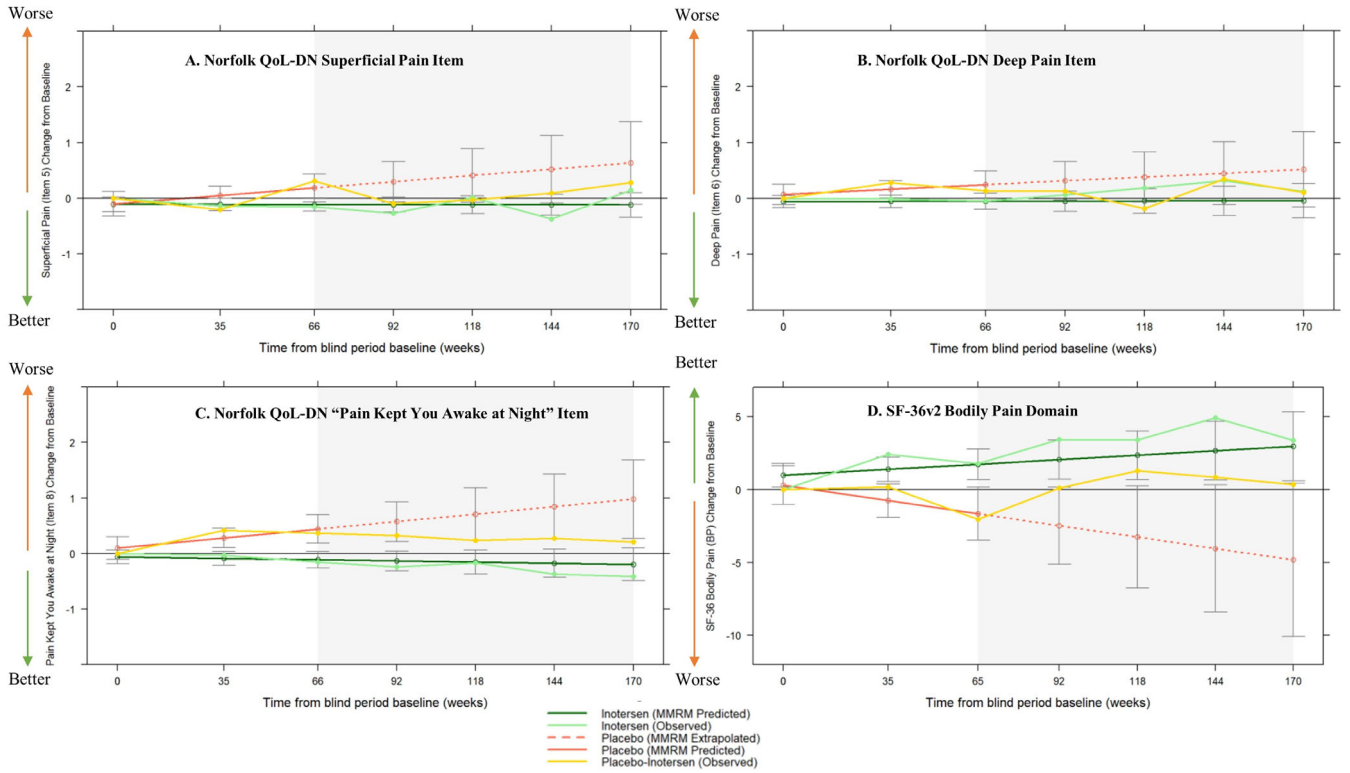

FIGURE 3 Observed and mixed-effects models with repeated measures (MMRM)-predicted changes from baseline in selected pain-related subdomain and item scores of Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN)[1] and 36-item Short Form Health Survey version 2 (SF-36v2).[2] Gray bars represent 95% confidence intervals for the MMRM-predicted means. Shading indicates the open-label extension period. [1] A total of 163 patients had non-missing baseline Norfolk QoL-DN total scores and were used in the analysis of Norfolk QoL-DN outcomes. [2] A total of 164 patients had non-missing baseline SF-36v2 PCS scores and were used in the analysis of SF-36v2 outcomes.

inotersen arm and the MMRM-extrapolated placebo arm favored inotersen, and was statistically significant at weeks 35 and 66, but not during the OLE period.

The Norfolk QoL-DN "Pain kept you awake at night" item is presented in Figure 3C. The difference in scores between the MMRM-predicted inotersen arm and the MMRM-extrapolated placebo arm was statistically significant at all follow-up time-points of interest. After 170 weeks, patients in the placebo-inotersen group had worse HRQL, with a mean increase in item score of 0.98 (SE, 0.36), whereas inotersen-inotersen patients had slightly improved HRQL, with a decrease in item score of 0.19 (SE, 0.15). At week 170, the difference between the two arms was −1.17 ($P < .01$).

The SF-36v2 BP domain is presented in Figure 3D. The difference in scores between the MMRM-predicted inotersen arm and the MMRM-extrapolated placebo arm was also statistically significant at all follow-up time points of interest. After 170 weeks, patients in the placebo-inotersen group had worse expected HRQL with a mean MMRM-predicted decrease in the SF-36v2 BP score of 4.82 (SE, 2.67), whereas the inotersen-inotersen patients had improved HRQL, with a mean MMRM-predicted increase in the SF-36v2 BP score of 2.96 (SE, 1.19); the difference between the two arms was 7.78 ($P < .01$).

3.3.4 | Patient functioning outcomes

The Norfolk QoL-DN PF/LFN subdomain is presented in Figure 4A. The extrapolated difference in scores between the MMRM-predicted inotersen arm and the MMRM-extrapolated placebo arm was statistically significant at all follow-up time-points of interest. After 170 weeks, the patients in the placebo-inotersen group were expected to have substantially worse HRQL, with a mean MMRM-predicted increase in the Norfolk QoL-DN PF/LFN subdomain score of 15.86 (SE, 3.53). Patients in the inotersen-inotersen group had a slight decrease in HRQL, with a mean MMRM-predicted increase of 3.49 (SE, 1.91) in Norfolk QoL-DN PF/LFN score; the extrapolated difference between the two arms was −12.37 ($P < .01$).

The Norfolk QoL-DN ADL subdomain is presented in Figure 4B. The extrapolated difference between the MMRM-predicted inotersen-inotersen and placebo-inotersen arms was statistically significant at all follow-up time-points of interest. After 170 weeks, patients in the placebo-inotersen group were expected to have substantially worse HRQL, with a mean increase in MMRM-predicted Norfolk QoL-DN ADL subdomain score of 6.75 (SE, 1.17), whereas patients in the inotersen-inotersen group had a slight worsening of HRQL, with a mean increase of 2.12 (SE, 0.66) in MMRM-predicted Norfolk QoL-DN ADL score; the difference between the two arms was −4.64 ($P < .001$).

The SF-36v2 PF domain is presented in Figure 4C. The difference in scores between the MMRM-predicted inotersen arm and the MMRM-extrapolated placebo arm was statistically significant at all follow-up time-points of interest. After 170 weeks, patients in the placebo-inotersen group were expected to have substantially worse HRQL, with a mean decrease in SF-36v2 PF score of 12.96 (SE, 2.31), whereas inotersen-inotersen patients' HRQL worsened slightly, with a mean decrease in SF-36v2 PF score of 2.41 (SE, 1.08); the difference between the two arms was 10.55 ($P < .01$).

The SF-36v2 RP domain is presented in Figure 4D. The difference in scores between the MMRM-predicted inotersen arm and the MMRM-extrapolated placebo arm was statistically significant at all follow-up time-points of interest. After 170 weeks, the placebo-inotersen patients' HRQL was expected to deteriorate substantially, with a mean decrease in the SF-36v2 RP score of 9.85 (SE, 2.76), whereas the inotersen-inotersen patients' HRQL worsened slightly, with a mean decrease in SF-36v2 RP score of 1.09 (SE, 1.07); the difference between the two arms was 8.76 ($P < 0.01$).

4 | DISCUSSION

This long-term post-hoc analysis of patients who participated in the NEURO-TTR trial and its subsequent OLE has demonstrated that those receiving inotersen-inotersen therapy deteriorated significantly slower across functional and HRQL measures compared with extrapolated placebo patients consistently up to 170 weeks. In addition, patients in the inotersen-inotersen group showed improvements in several pain measures. The difference in the predicted change from baseline among patients in the inotersen-inotersen group and the extrapolated placebo patients remained statistically significant at 170 weeks for the Norfolk QoL-DN total score, including the PF/LFN, ADL, and S subdomains and the "Pain kept you awake at night" item score, and the SF-36v2 PCS domain scores, including PF, RP, and BP. Although the symptoms of hATTR-PN were attenuated by inotersen treatment beginning at week 66, patients receiving placebo-inotersen showed consistently worse HRQL compared with patients who received inotersen-inotersen, despite switching from placebo to inotersen at week 66.

In the NEURO-TTR phase III clinical trial, inotersen modified the course of neuropathy and led to significant improvement in HRQL at 65 weeks in patients with hATTR, and patients gained benefit from treatment across TTR mutation types, disease stages, and presence or absence of cardiomyopathy at baseline.[16] Our findings align with those of a recent qualitative analysis of the OLE data by Yarlas et al,[21] and further contribute to our understanding of the effects of long-term inotersen treatment on HRQL in patients with hATTR-PN. We found that treatment resulted in a statistically significant delay in the long-term deterioration of key

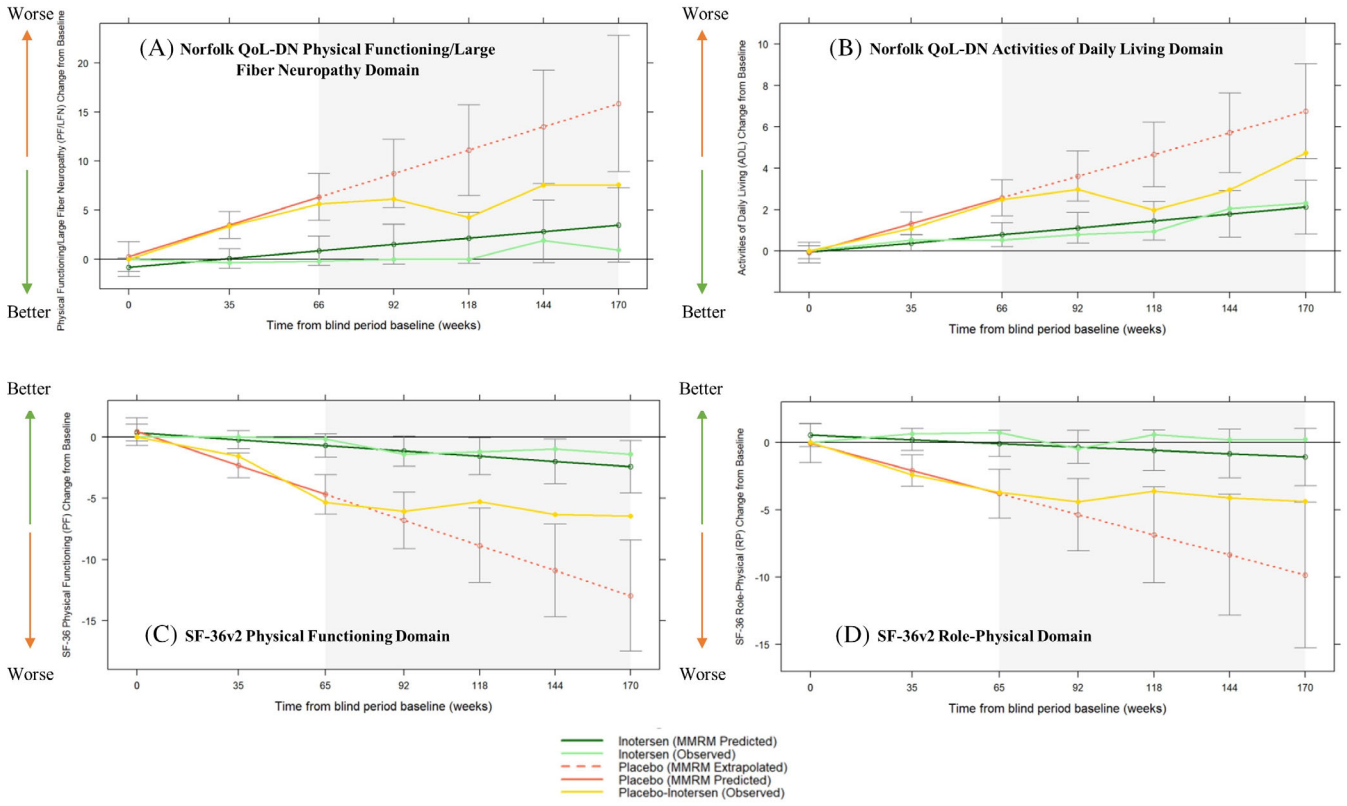

FIGURE 4 Observed and mixed-effects models with repeated measures (MMRM)-predicted changes from baseline in selected physical functioning domains of the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN)[1] and 36-item Short Form Health Survey version 2 (SF-36v2).[2] Gray bars represent 95% confidence intervals for the MMRM predicted means. Shading indicates the open-label extension period. A total of 163 patients had non-missing baseline Norfolk QoL-DN total scores and were used in the analysis of Norfolk QoL-DN outcomes. A total of 164 patients had non-missing baseline SF-36v2 PCS scores and were used in the analysis of SF-36v2 outcomes.

outcomes, particularly measures related to physical functioning and the majority of key pain measures. Importantly, raw item scores were analyzed using MMRM to provide an extrapolation of the trajectory of the placebo group patients over the duration of the OLE period had they not received treatment with inotersen. The comparison with placebo is critical in understanding the magnitude of long-term deterioration that can occur in ATTR, as well as the continued benefit provided by inotersen treatment that results in substantial slowing of disease progression, likely outweighing the potential risks of adverse side effects which are well-controlled with active monitoring.[16]

A small number of recent studies addressed the impact of inotersen treatment on HRQL of the patients enrolled in the NEURO-TTR trial using various HRQL measures, and those findings were largely in agreement with ours. In their 2020 study, Coelho et al found that several domains on the Norfolk QoL-DN and the SF-36v2 were stable or showed improvements from baseline to 66 weeks in patients treated with inotersen, and the effects were more pronounced for PF, RP, BP, Social Functioning, and RE domains.[26] In contrast, patients receiving placebo frequently exhibited clinically meaningful worsening on their Norfolk QoL-DN total scores and also for ADL, PF/LFN, and S domain scores. Dyck et al conducted two post-hoc analyses to assess the effect of inotersen treatment on HRQL in patients enrolled in the NEURO-TTR trial using the mNIS+7 neurophysiological/Lower Limb Function (LLF) testing and the Neuropathy Symptom and Change (NSC) score.[27,28] The authors found that treatment with inotersen stabilized symptom severity across all major mNIS+7 components, LLF, and all subdomains of the NSC when compared with placebo. In addition, inotersen reduced upper and lower limb weakness,[27] which parallels findings from the NEURO-TTR trial, whereby inotersen treatment reduced progression of the mNIS "weakness" subcomponent. Inotersen treatment also showed benefit in attenuating the severity of positive neuropathic sensory and positive pain symptoms, as measured by the subdomain scores on the NSC assessment; this finding contrasted with placebo treatment, which was associated with worsening HRQL from baseline to week 66. Together, this promising evidence suggests that inotersen may not only slow hATTR symptom progression, but may also alleviate the baseline severity of some symptoms. The physical burden becomes increasingly more profound in patients with hATTR as they progress further in the course of the disease,[3,8,9] which underscores the importance of initiating early treatment with effective therapies, such as inotersen, to preserve HRQL in this fragile population.

4.1 | Limitations

Our study is subject to certain limitations. First, while the well-fitting linear trend up to week 65/66 suggests that the extrapolation of effects in the placebo arm is reasonable, it is possible that nonlinear trends could occur over longer term follow-up on placebo; thus, extrapolations should be interpreted with caution. Second, the responder definition thresholds for the Norfolk QoL-DN total score have only recently been estimated,[29] and interpretation of these thresholds needs further examination. In addition, the Norfolk QoL-DN domain and item scores may also be challenging to interpret. This is especially true for the pain items, as patient responses were limited to a discrete range of possible scores. Finally, the loss of patients during the OLE period may have led to insufficient power to detect statistically significant effects in several Norfolk QoL-DN items.

There are additional limitations inherent to the NEURO-TTR trial,[16] such as the exclusion of patients with end-stage disease. Furthermore, some imbalances in trial arms were unavoidable. For instance, patients who were assigned inotersen had more advanced autonomic and sensorimotor neuropathy and a longer mean duration of hATTR polyneuropathy from diagnosis than those assigned to placebo. A greater proportion of patients receiving inotersen also had cardiomyopathy at trial entry and a longer duration from the onset of cardiomyopathy symptoms.

5 | CONCLUSIONS

Inotersen treatment significantly delayed the long-term deterioration of key HRQL outcomes among patients with hATTR-PN, and the benefits were particularly evident for measures related to physical functioning and key pain measures. In some cases, inotersen treatment was potentially associated with halting or reversal of the decline in HRQL. Given the significant burden associated with hATTR-PN on patients and their caregivers, improving HRQL remains a crucial goal to be considered when managing the disease. The data continue to confirm that treatment resulting in TTR reduction preserves functionality and quality of life in patients with hATTR for more than 3 years.

ACKNOWLEDGMENTS

Medical writing assistance was provided by Loraine Georgy, PhD, an employee of Analysis Group, Inc, a consulting company that provided paid consulting services to Ionis Pharmaceuticals/Akcea Therapeutics, Inc, which funded the development and conduct of this study and manuscript.

CONFLICTS OF INTEREST

C.K. reports consulting/educational activities for Ionis Pharmaceuticals/Akcea Therapeutics, Inc, Alexion, Alnylam, Argenx, Biogen, CSL Behring, Medscape, and Sanofi Genzyme, and has received research grants from Sanofi Genzyme and Ionis Pharmaceuticals/Akcea Therapeutics. M.V.L. and D.B. are employees and stockholders of Ionis Pharmaceuticals/Akcea Therapeutics; A.B. was an employee and stockholder of Ionis Pharmaceuticals/Akcea Therapeutics at the time of the study. M.Y., N.D., and A.G. are employees of Analysis Group, a consultancy firm that received payment from Ionis Pharmaceuticals/Akcea Therapeutics for the conduct of this study. At the time of the study, J.J.Z. was an employee of Analysis Group, which received payment from Ionis Pharmaceuticals/Akcea Therapeutics, for the conduct of this study.

FUNDING INFORMATION

The funder of this study, Ionis Pharmaceuticals/Akcea Therapeutics, Inc, participated in study design, research, analysis, data collection and interpretation, and approved the manuscript for publication.

DATA AVAILABILITY STATEMENT

The data presented in this study are available upon reasonable request from the corresponding author.

ETHICAL APPROVAL STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Chafic Karam https://orcid.org/0000-0003-3868-2994
Nicolae Done https://orcid.org/0000-0001-6517-646X

REFERENCES

1. Plante-Bordeneuve V. Transthyretin familial amyloid polyneuropathy: an update. *J Neurol*. 2018;265:976-983.
2. Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: current perspectives on improving patient care. *Ther Clin Risk Manag*. 2020;16:109-123.
3. Yarlas A, Gertz MA, Dasgupta NR, et al. Burden of hereditary transthyretin amyloidosis on quality of life. *Muscle Nerve*. 2019;60:169-175.
4. Coelho T, Maurer MS, Suhr OB. THAOS---the transthyretin amyloidosis outcomes survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr Med Res Opin*. 2013;29:63-76.
5. Stewart M, Shaffer S, Murphy B, et al. Characterizing the high disease burden of transthyretin amyloidosis for patients and caregivers. *Neurol Ther*. 2018;7:349-364.
6. Ines M, Coelho T, Conceicao I, Ferreira L, Carvalho M, Costa J. Transthyretin familial amyloid polyneuropathy impact on health-related quality of life. *Orphanet J Rare Dis*. 2015;10(Suppl 1):O28.
7. Lovley A, Raymond K, Guthrie SD, Pollock M, Sanchorawala V, White MK. Patient-reported burden of hereditary transthyretin amyloidosis on functioning and well-being. *J Patient Rep Outcomes*. 2021;5:3.
8. Danoncourt RN, Adams D, Gonzalez-Duarte A, et al. Burden of illness for patients with hereditary ATTR amyloidosis with polyneuropathy begins with symptom onset and increases with disease progression. *Value Health*. 2016;19:A436.
9. Adams D, Amitay O, Coelho T. Patients with hereditary ATTR amyloidosis experience an increasing burden of illness as the disease progresses. *Orphanet J Rare Dis*. 2015;10(Suppl 1):P58.
10. Gertz MA, Mauermann ML, Grogan M, Coelho T. Advances in the treatment of hereditary transthyretin amyloidosis: a review. *Brain Behav*. 2019;9:e01371.
11. Ines M, Coelho T, Conceicao I, Ferreira L, de Carvalho M, Costa J. Health-related quality of life in hereditary transthyretin amyloidosis polyneuropathy: a prospective, observational study. *Orphanet J Rare Dis*. 2020;15:67.
12. Coelho T, Vinik A, Vinik EJ, Tripp T, Packman J, Grogan DR. Clinical measures in transthyretin familial amyloid polyneuropathy. *Muscle Nerve*. 2017;55:323-332.
13. 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;19:104-114.
14. Mathew V, Wang AK. Inotersen: new promise for the treatment of hereditary transthyretin amyloidosis. *Drug Des Devel Ther*. 2019;13:1515-1525.
15. Crooke ST, Baker BF, Crooke RM, Liang X-h. Antisense technology: an overview and prospectus. *Nat Rev Drug Discov*. 2021;20:427-453.
16. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:22-31.
17. Mahfouz M, Maruyama R, Yokota T. Inotersen for the treatment of hereditary transthyretin amyloidosis. *Methods Mol Biol*. 2020;2176:87-98.
18. Brannagan TH, Wang AK, Coelho T, et al. Early data on long-term efficacy and safety of inotersen in patients with hereditary transthyretin amyloidosis: a 2-year update from the open-label extension of the NEURO-TTR trial. *Eur J Neurol*. 2020;27:1374-1381.
19. Benson MD, Dasgupta NR, Rao R. Diagnosis and screening of patients with hereditary transthyretin amyloidosis (hATTR): current strategies and guidelines. *Ther Clin Risk Manag*. 2020;16:749-758.
20. Gendre T, Plante-Bordeneuve V. Strategies to improve the quality of life in patients with hereditary transthyretin amyloidosis (hATTR) and autonomic neuropathy. *Clin Auton Res*. 2019;29(Suppl 1):25-31.
21. Yarlas A, Lovley A, McCausland K, et al. Early data on long-term impact of Inotersen on quality-of-life in patients with hereditary transthyretin amyloidosis polyneuropathy: open-label extension of NEURO-TTR. *Neurol Ther*. 2021;10:865-886.
22. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. *Nat Rev Neurol*. 2019;15:387-404.
23. Vinik EJ, Hayes RP, Oglesby A, et al. The development and validation of the Norfolk QOL-DN, a new measure of patients' perception of the effects of diabetes and diabetic neuropathy. *Diabetes Technol Ther*. 2005;7:497-508.
24. Maruish ME. *User's Manual for the SF-36v2 Health Survey*. QualityMetric; 2011.
25. Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA*. 2013;310:2658-2667.
26. Coelho T, Yarlas A, Waddington-Cruz M, et al. Inotersen preserves or improves quality of life in hereditary transthyretin amyloidosis. *J Neurol*. 2020;267:1070-1079.
27. Dyck PJB, Coelho T, Waddington Cruz M, et al. Neuropathy symptom and change: inotersen treatment of hereditary transthyretin amyloidosis. *Muscle Nerve*. 2020;62:509-515.
28. Dyck PJB, Kincaid JC, Wiesman JF, et al. mNIS+7 and lower limb function in inotersen treatment of hereditary transthyretin-mediated amyloidosis. *Muscle Nerve*. 2020;62:502-508.
29. Yarlas A, Lovley A, Brown D, Kosinski M, Vera-Llonch M. Responder analysis for neuropathic impairment and quality-of-life assessment in patients with hereditary transthyretin amyloidosis with polyneuropathy in the NEURO-TTR study. *J Neurol*. 2021;269:1-13.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Karam C, Brown D, Yang M, et al. Long-term treatment effects of inotersen on health-related quality of life in patients with hATTR amyloidosis with polyneuropathy: Analysis of the open-label extension of the NEURO-TTR trial. *Muscle & Nerve*. 2022;1-9. doi:10.1002/mus.27675