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Factors associated with increased health-related quality-of-life benefits in hereditary transthyretin amyloidosis polyneuropathy patients treated with inotersen

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Abstract

Introduction/Aims: Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) is a genetic condition associated with significant morbidity and mortality. In this study we aimed to identify patient subgroups exhibiting the greatest health-related quality of life (HRQL) benefit from inotersen treatment.

Methods: We examined data from the inotersen phase 2/3 randomized, controlled trial for ATTRv-PN, NEURO-TTR (NCT01737398, 66 weeks). LASSO regression models predicted changes in Norfolk QoL-DN total score (TQoL, range −4 to 136; higher scores indicate poorer HRQL) from baseline in the inotersen and placebo arm, respectively. Individualized efficacy scores (ES) were calculated as differences between predicted change scores had patients received inotersen vs placebo. Patients were ranked by ES to define the greatest-benefit subpopulation (top 50%). Characteristics of the top 50% and bottom 50% of patients were compared.

Results: The overall mean ± standard deviation TQoL change was −0.20 ± 19.13 for inotersen (indicating no change) and 10.77 ± 21.13 for placebo (indicating deterioration). Within the highest-benefit patients, mean TQoL change was −11.03 ± 17.06 (improvement) for inotersen and 11.24 ± 22.97 (deterioration) for placebo ($P < .001$). Compared with the overall population, patients in the greatest-benefit subpopulation were younger, more likely to have polyneuropathy disability (PND) scores 1 or 2, less likely to have received prior tafamidis or diflunisal treatment, and more likely to have Val30Met mutations and higher (worse) baseline TQoL.

Conclusions: Patients who were younger and/or at earlier polyneuropathy stages experienced greater HRQL benefits from inotersen over 66 weeks. These findings underscore the need for early diagnosis and treatment initiation, especially among more severely affected patients in early stages of ATTRv-PN.

Abbreviations: BMI, body mass index; ES, patient-level efficiency score; ATTRv, hereditary transthyretin amyloidosis; ATTRv-CM, hereditary transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; HRQL, health-related quality of life; KPS, Karnofsky performance status; LASSO, least absolute shrinkage and selection operator; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score+7; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PND, polyneuropathy disability; QoL-DN, Quality of Life–Diabetic Neuropathy; TQoL, total quality of life (score); TTR, transthyretin.

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KEYWORDS
health-related quality of life, hereditary transthyretin amyloidosis, individualized medicine, inotersen, polyneuropathy

1 | INTRODUCTION

Hereditary transthyretin amyloidosis (ATTRv) is a disorder caused by mutations in the gene encoding for transthyretin (TTR) protein, resulting in amino acid changes that destabilize native protein folding.[1–3] A predominant clinical feature of ATTRv is progressive length-dependent axonal polyneuropathy (ATTRv-PN), commonly associated with autonomic dysfunction.[1–3] The most common genetic variant associated with polyneuropathy is the Val30Met mutation (148G→A), which is responsible for approximately 50% of *TTR* variants worldwide.[2–4] Other *TTR* mutations found with different frequencies across geographic regions include mutations resulting predominantly in polyneuropathy, such as Ser77Tyr, Val28Met, and Ile107Pro; mutations associated with predominant cardiomyopathy, such as Val122Ile, Ile84Ala, or Gly65Leu; and mutations with a mixed phenotype, such as Thr60Ala, Thr49Ala, and others.[2,5–7] Patients with ATTRv-PN experience substantially reduced health-related quality of life (HRQL) due to disease symptoms and associated disabilities,[8–10] which often correlate with the specific *TTR* mutation.[11] Furthermore, a progressive decline in HRQL with longer disease duration and greater severity has been observed using the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QoL-DN) questionnaire.[12,13] Several clinical trials for ATTRv have included the Norfolk QoL-DN as a key efficacy endpoint, indicating its importance in assessing the benefit of therapies for this disease.[14–16]

Historically, therapeutic options for ATTRv-PN have been scarce.[5,17–21] More recently, inotersen was approved for the treatment of adults with ATTRv-PN in multiple countries.[22–24] This antisense oligodeoxynucleotide binds to the TTR messenger RNA and suppresses the hepatic production of both mutated and wild-type TTR protein.[21] In the randomized, controlled phase 2/3 trial NEURO-TTR (NCT01737398 at ClinicalTrials.gov), patients with ATTRv-PN treated with inotersen experienced significantly delayed neurological disease progression and improved HRQL compared with patients treated with placebo.[14]

Previous evidence suggests that untreated patients experience progressive deterioration of HRQL, whereas treated patients may experience improved or preserved HRQL over time.[10] However, the aggressive course of the disease and high heterogeneity of the ATTRv-PN patient population continue to pose challenges in clinical practice[25,26] and scientific research.[27] Over the past 20 years, there has been a growing awareness of the importance of individualized medicine across multiple disease areas.[28,29] Using an individualized medicine approach first proposed by Cai et al[30] and further developed by Zhao et al,[31] the primary objective of this study was to identify distinct patient subgroups from the NEURO-TTR trial population that exhibited the greatest degree of near-term benefit from inotersen treatment, as measured by changes in Norfolk QoL-DN score. Furthermore, the present analysis aimed to include factors previously identified as potential significant predictors of change in HRQL.[14,32]

2 | METHODS

2.1 | Data sources

Data from NEURO-TTR, an international, randomized, double-blind, placebo-controlled, 15-month, phase 2/3 trial of inotersen in patients with ATTRv-PN, were used for this analysis.[14] A total of 173 patients were randomly assigned in the trial, in a 2:1 ratio, to receive weekly subcutaneous injections of inotersen (300 mg) or placebo (one patient was randomized by mistake, did not receive any dose in the trial, and was excluded from subsequent interventions and analyses). The three randomization strata based on data from the electronic case report form included: Val30Met TTR mutation status (yes or no); ATTRv-PN disease stage (Coutinho stage 1 [no ambulatory assistance required] or stage 2 [assistance with ambulation required]); and previous treatment status (tafamidis or diflunisal vs none). The use of medications approved for the treatment of ATTRv-PN during the trial period, including tafamidis or diflunisal, was prohibited. In the NEURO-TTR trial, the primary endpoints were Norfolk QoL-DN total score (TQoL) and modified Neuropathy Impairment Score+7 (mNIS+7) captured at baseline, week 35, and week 66. In this study we focused on analyzing changes in Norfolk QoL-DN TQoL score from baseline to week 66.

As described by Benson et al,[14] the NEURO-TTR trial protocol was approved by institutional review boards or local ethics committees. All patients provided written informed consent to participate in the trial.

2.2 | Study population

Adult patients were required to have an mNIS+7 score of 10 to 130, a TTR mutation determined by genotyping, and documented amyloid deposits determined via biopsy. Patients were excluded if they had clinically significant abnormalities in screening laboratory values, a Karnofsky performance status (KPS) score of 50 or less, other causes of polyneuropathy besides ATTRv, previous liver transplantation, heart failure of New York Heart Association (NYHA) class III or higher, or received tafamidis or diflunisal (ie, medications approved for the treatment of ATTRv-PN) during the trial period.

2.3 | Outcome measures

The Norfolk QoL-DN questionnaire is a patient-reported outcome measure that was designed to capture the impact of neuropathy symptoms on QoL experienced by diabetic neuropathy patients,[33] and subsequently validated for use in patients with ATTRv-PN.[13] The Norfolk QoL-DN provides a total score (ie, TQoL) ranging from −4 to

136 based on all items, with higher scores indicating worse functioning and poorer HRQL. The outcome of interest in the present study was the change in TQoL from baseline to week 66, with a negative change indicating an improvement in HRQL and a positive change indicating a worsening.

2.4 | Selection of candidate predictors

This investigation was a post hoc analysis of the phase 2/3 NEURO-TTR trial data. Among the large number of available baseline characteristics in the trial, a subset of 18 candidate predictors was identified based on clinical relevance and independent expert input (three contributors). Demographics included age and sex, and body measurements included weight, body mass index (BMI), and modified BMI (mBMI). Because BMI may not accurately reflect fluid accumulation, mBMI (the product of BMI and serum albumin concentration) is generally considered a more appropriate measure of disease progression in ATTRv-PN patients.[34] Disease characteristics included validated staging systems such as the Coutinho score (stage 1 vs 2) and the PND score (0 to 4), which are largely based on ambulation.[35] Other disease characteristics included baseline Norfolk QoL-DN TQoL score, duration from ATTRv-PN diagnosis, duration from onset of ATTRv-PN symptoms, previous treatment with diflunisal or tafamidis (yes/no), diagnosis of ATTRv with cardiomyopathy (yes/no), NYHA score (I vs II), KPS score, TTR genotype (Val30Met, Ser77Tyr, Thr60Ala, Leu58His, other), TTR concentration, and N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) concentration. Only year and month were collected for diagnosis of ATTRv-PN and onset of ATTRv-PN symptoms. Durations from diagnosis and from onset of symptoms were calculated relative to the date of informed consent.

2.5 | Statistical methods

Two linear regression models with least absolute shrinkage and selection operator (LASSO) regularization were fitted, one for each of the treatment groups (inotersen and placebo), with change from baseline to week 66 in Norfolk QoL-DN TQoL as the outcome variable. Baseline characteristics were included as covariates, and the LASSO regularization selected only the covariates that strongly predict the outcome variable; a null model (intercept-only) was selected for the placebo arm. The LASSO procedure automatically selected the most statistically relevant predictors by penalizing (shrinking) the regression model coefficients via a penalty term. The degree of penalization was governed by a regularization parameter, with a value selected to minimize prediction error through a tenfold cross-validation procedure, thus achieving a balance between model overfitting and underfitting and reducing reliance on model assumptions. The LASSO regularization method allowed selection of the strongest predictors of the outcome variable from a large predictor set given the small sample size, in a way that increases generalizability of the findings to other data sets.

Based on these prediction models, a patient-level efficacy score (ES) was defined and estimated as the expected treatment difference conditional on covariates, including only the predictors selected by LASSO. In particular, the individualized ES for a given patient was calculated as the difference between the predicted change in the outcome if treated with inotersen and the predicted change if treated with placebo, conditional on patients' selected predictors at baseline. Therefore, the ES reflects the expected benefit of treatment relative to placebo for an individual patient given their baseline characteristics.[31]

Patients were subsequently ranked based on their individualized ES from highest to lowest, corresponding to the largest expected treatment effect to the smallest. Subgroups with higher benefit were defined based on quantiles of the ES distribution, that is, top 5%, top 10%, etc. The average ES in these subgroups was then assessed and used to determine the extent to which treatment effects varied across the patient population. To demonstrate the differences in patients' characteristics, we compared the "top" 50% and "bottom" 50% with respect to expected treatment benefit.

Differences in mean baseline characteristics between treatment groups and between segments of patients with higher vs lower than median efficacy scores were assessed using analysis of variance (ANOVA) for continuous variables and the chi-square tests for categorical variables. *P* values reported based on ANOVA and chi-square tests were statistically significant at the $\alpha = 0.05$ level. Only patients who had complete data for all outcomes measured were included in the analysis.

3 | RESULTS

3.1 | Study population

Starting with the 172 patients in NEURO-TTR who had received at least one dose of the trial regimen, in the present study sample we excluded 31 patients in the inotersen arm and 8 patients in the placebo arm due to missing values for at least 1 of the 18 candidate predictors for the outcome. The final analytical sample consisted of 133 patients, with 81 patients in the inotersen arm and 52 patients in the placebo arm. Among the included patients, the values of baseline characteristics were generally comparable between treatment groups (Table 1).

3.2 | Prediction models

The estimated coefficients for the 11 predictors selected by LASSO in the model fitted in the inotersen arm are presented in Table 2. Positive coefficients indicate that a higher value of the predictor is associated with a lower predicted benefit on TQoL of inotersen. Notably, patients with a lower benefit gained on TQoL are those who were older, with disease stage 2 or with a higher PND score, with previous diflunisal or tafamidis treatment, and with a Ser77Tyr mutation.

TABLE 1 Descriptive statistics for candidate predictors

Baseline characteristics	Inotersen (N = 81)	Placebo (N = 52)	*P* value
Demographics			
Age (years)	59.37 ± 11.76	59.40 ± 14.38	.99
Sex			.84
Female	26 (32.10%)	15 (28.85%)	
Male	55 (67.90%)	37 (71.15%)	
Weight (kg)	71.65 ± 17.65	71.98 ± 18.68	.92
Height (cm)	171.75 ± 8.56	171.53 ± 9.04	.89
Modified BMI [$(kg/m^2) \times (g/L)$]	1025.87 ± 224.57	1053.68 ± 231.01	.49
BMI (kg/m^2)	24.12 ± 4.77	24.24 ± 4.90	.90
Randomization stratum			
Disease stage for randomization stratum			.91
Stage 1	54 (66.67%)	36 (69.23%)	
Stage 2	27 (33.33%)	16 (30.77%)	
Previous treatment for randomization stratum			.31
N	29 (35.80%)	24 (46.15%)	
Y	52 (64.20%)	28 (53.85%)	
Disease characteristics			
Duration of disease from ATTRv-PN diagnosis (months)	43.57 ± 53.45	39.35 ± 41.23	.63
Duration from onset of ATTRv-PN symptoms (months)	63.32 ± 49.38	64.63 ± 55.47	.89
Diagnosed with ATTRv-CM			>.99
N	49 (60.49%)	31 (59.62%)	
Y	32 (39.51%)	21 (40.38%)	
PND score			.75
1	24 (29.63%)	20 (38.46%)	
2	30 (37.04%)	16 (30.77%)	
3	23 (28.40%)	13 (25.00%)	
4	4 (4.94%)	3 (5.77%)	
NT-proBNP (pmol/L)	91.27 ± 152.89	87.29 ± 169.16	.89
NYHA score			.86
I	52 (64.20%)	35 (67.31%)	
II	29 (35.80%)	17 (32.69%)	
KPS score	76.67 ± 10.84	76.73 ± 11.15	.97
TTR genotype (top 4 mutations)			.24
Val30Met	38 (46.91%)	30 (57.69%)	
Thr60Ala	10 (12.35%)	8 (15.38%)	
Leu58His	7 (8.64%)	3 (5.77%)	
Ser77Tyr	3 (3.70%)	4 (7.69%)	
Other	23 (28.40%)	7 (13.46%)	
TTR concentration (g/L)	0.22 ± 0.07	0.22 ± 0.05	.67
Blind period baseline HRQL			
Norfolk QoL-DN TQoL score	46.90 ± 25.71	48.86 ± 26.91	.67

Abbreviations: BMI, body mass index; CM, cardiomyopathy; ATTRv, hereditary transthyretin amyloidosis; HRQL, health-related quality of life; KPS, Karnofsky performance status; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PND, polyneuropathy disability; QoL-DN TQoL, Quality of Life-Diabetic Neuropathy total quality-of-life score; TTR, transthyretin.

TABLE 2 Coefficients from linear regression models with LASSO selection of change from baseline in Norfolk QoL-DN TQoL score in the inotersen treatment arm (N = 81)

Baseline characteristics	Coefficients
Intercept	−58.587
Demographics	
Age (years)	0.397
Height (cm)	0.289
mBMI [(kg/m^2) × (g/L)]	−0.008
Randomization strata	
Previous treatment with diflunisal or tafamidis	4.907
Disease characteristics	
Duration from onset of ATTRv-PN symptoms (months)	0.025
PND score	2.682
NT-proBNP (pmol/L)	0.001
KPS score	−0.089
TTR genotype	
Val30Met	Reference
Ser77Tyr	6.157
Other	−0.399
TTR concentration (g/L)	−9.847
Blind period baseline	
Norfolk QoL-DN TQoL	−0.172

Abbreviations: BMI, body mass index; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; KPS, Karnofsky performance status; LASSO, least absolute shrinkage and selection operator; mBMI, modified body mass index; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PND, polyneuropathy disability; QoL-DN TQoL, Quality of Life–Diabetic Neuropathy total quality-of-life score; TTR, transthyretin.

Patients with rarer mutations and higher mBMI, KPS score, and baseline Norfolk QoL-DN score had a better response to inotersen on average (Table 2). Thus, it could be concluded with reasonable confidence that these baseline characteristics have a significant predictive effect of higher inotersen benefit. In the placebo arm, the LASSO linear regression model selected no predictors (ie, an intercept-only model), indicating that none of the candidate baseline characteristics was effective in predicting change in Norfolk QoL-DN TQoL score. As a result, the mean outcome value in the placebo arm was the best predictor of treatment benefit (Table 2).

3.3 | Assessment of higher benefit subgroups

The estimated week 66 changes in Norfolk QoL-DN TQoL score for subgroups of patients treated with inotersen and placebo are displayed in Figure 1A. Treating the full population with inotersen was associated with an approximately 11-point incremental improvement in TQoL, compared with placebo. The difference in scores among different subgroups highlights the heterogeneity in the level of benefit patients experience, which is discerned by the model based on their baseline characteristics. The top responders, as ranked by the prediction model, had a greater observed benefit from treatment (smaller subgroups) compared with the bottom responders, which is illustrated by the average benefit declining as more patients with low benefit are included in the subgroups. Inotersen patients showed greater heterogeneity in their responses relative to placebo patients. For example, the top 10% of patients with the largest ES (who were predicted to benefit most) experienced a 19-point average improvement in Norfolk QoL-DN TQoL score associated with inotersen relative to placebo. In contrast, the patients in the control group all deteriorated by roughly the same amount (10-point decrease), in a manner that could be predicted based on their baseline characteristics (Figure 1A). The same trend is also illustrated in Figure 1B, which displays the estimated difference in changes in Norfolk QoL-DN TQoL score between inotersen and placebo across subgroups of patients. In smaller subgroups, this elevation could be partially explained by random variations, as represented by the wider 95% confidence intervals.

When comparing the top 50% responders vs the bottom 50% responders, several key baseline characteristics were statistically significantly different (Table 3). The top 50% responders were significantly younger than the bottom 50% responders, with a higher proportion of patients in disease stage 1, and a lower proportion of patients with previous treatment. Top 50% responders had higher proportions of patients with PND scores 1 and 2, and lower proportions of patients with PND scores of 3 and 4, compared with the bottom 50% responders. The top 50% responders also had a different profile of genetic mutations compared with the bottom 50% responders, with Ser77Tyr, Thr60Ala, and Leu58His being underrepresented, and Val30Met mutations being somewhat overrepresented among the top 50% responders. Finally, top 50% responders had a higher baseline Norfolk QoL-DN TQoL score compared with the bottom 50% responders.

4 | DISCUSSION

In this study, we found that the overall population of patients with ATTRv-PN from the NEURO-TTR trial population experienced significant HRQL benefits from inotersen. Our findings further suggest that the patient subgroups who showed the greatest near-term HRQL benefits from inotersen included those who were younger, less likely to have had previous treatment with tafamidis or diflunisal, and/or those experiencing earlier stages of polyneuropathy with worse HRQL at baseline.

Importantly, favorable responses to inotersen were still observed among patients with advanced disease, non-Val30Met mutations, and previous tafamidis or diflunisal use, although these benefits were not as large as those observed for the top 50% group. In contrast, previous evidence suggests that other ATTRv-PN treatments, such as liver transplantation and TTR stabilizers, may have more limited efficacy among patients with the aforementioned characteristics.[18,20] For instance, tafamidis has been shown to delay neurological disease progression and preserve HRQL among Val30Met carriers with stage

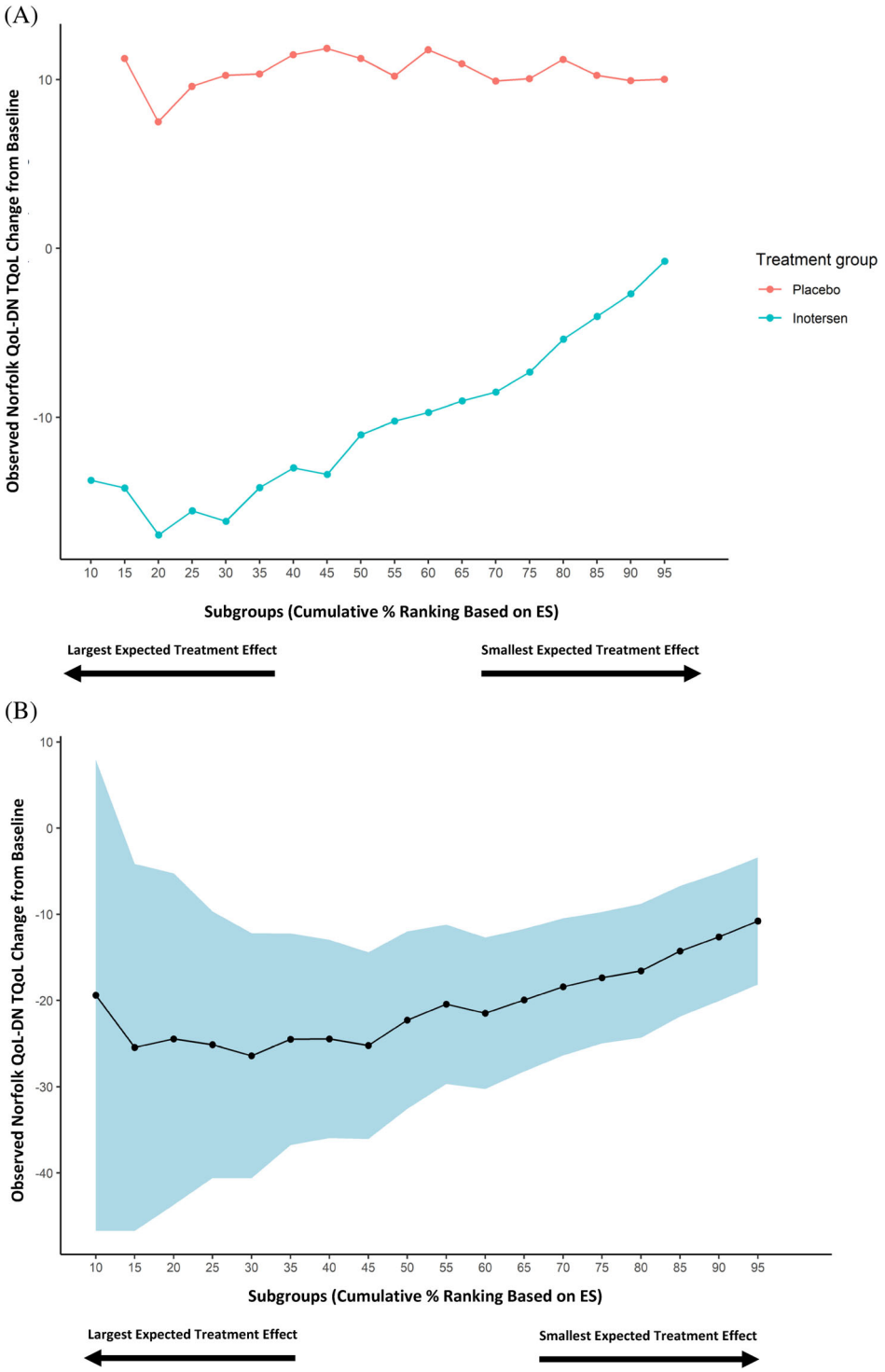

FIGURE 1 Week 66 changes in Norfolk QoL-DN total score with inotersen and placebo by subgroup. A, Estimated changes for subgroups of patients treated with inotersen or placebo. The subgroups on the x axis are cumulative percentile ranks constructed based on the estimated (ie, predicted) benefit using the LASSO model. Subgroups with smaller sizes represent the top responders (eg, top 10%) while subgroups with larger sizes represent bottom responders, as more patients with lower benefit are included. These subgroups are non-mutually exclusive (eg, the top 10% of responders are also included in top 15%). B, Estimated changes for subgroups of patients overall. ES, efficacy score; LASSO, linear regression models with least absolute shrinkage and selection operator; QoL-DN TQoL, Quality of Life–Diabetic Neuropathy total quality-of life-score.

1 disease,[15,36,37] whereas clinical benefits were less pronounced among patients with advanced disease or non-Val30Met mutations.[38,39] As a result, tafamidis is only approved for stage 1 symptomatic polyneuropathy in the European Union,[40,41] and it is not approved for hATTN-PN in the United States.[42] In addition, the non-steroidal anti-inflammatory drug diflunisal is currently being used off-label as a TTR stabilizer for polyneuropathy.[43] Diflunisal has been shown to delay the progression of neurological impairment and preserved HRQL in a trial with a clinically and genetically heterogeneous ATTRv-PN population.[44] Nonetheless, that study had a high attrition rate (52%) due to disease progression, which limits the interpretability of the findings. Taken together, this evidence suggests that inotersen may fill a major gap in the treatment landscape by addressing the unmet needs of patients with late-onset or advanced disease who may not be suitable candidates for other treatment classes. Further, inotersen may have an advantage over TTR stabilizers in later stages of disease due to its ability to potently suppress TTR production[21,45] and maintain the suppression with long-term treatment.[46]

TABLE 3 Differences in mean baseline characteristics between segments of patients with higher vs lower than median efficacy scores

Baseline characteristics (mean ± SD or %)	All patients	Patient segments based on estimated efficacy scores			
		Top 50% [A] N = 66	Bottom 50% [B] N = 67	Mean difference [A] – [B]	*P* value
Age	59.4 ± 12.8	51.9 ± 12.0	66.8 ± 8.6	−14.9 ± 1.8	<.001[a]
Male	69.2%	66.7%	71.6%	−5.0%	.66
Height (cm)	171.7 ± 8.7	170.9 ± 8.7	172.4 ± 8.8	−1.4 ± 1.5	.34
mBMI	1036.8 ± 226.6	1063.0 ± 243.2	1010.9 ± 207.6	52.1 ± 39.2	.19
Disease stage: stage 1 vs stage 2	67.7%	83.3%	52.2%	31.1%	<.001[a]
Previous treatment with tafamidis or diflunisal	60.2%	48.5%	71.6%	−23.2%	<.05[a]
Disease duration from ATTRv-PN diagnosis (months)	41.9 ± 48.9	43.2 ± 46.6	40.6 ± 51.4	2.6 ± 8.5	.76
Duration from onset of ATTRv-PN symptoms (months)	63.8 ± 51.6	57.9 ± 42.5	69.7 ± 59.0	−11.7 ± 8.9	.19
Diagnosed with ATTRv-CM	39.8%	33.3%	46.3%	−12.9%	.18
PND score					
1	33.1%	42.4%	23.9%	18.5%	
2	34.6%	40.9%	28.4%	12.6%	<.001[a]
3	27.1%	16.7%	37.3%	−20.6%	
4	5.3%	0.0%	10.4%	−10.4%	
NT-proBNP (pmol/L)	89.7 ± 158.8	72.5 ± 147.5	106.7 ± 168.6	−34.3 ± 27.5	.21
NYHA score I vs II	65.4%	63.6%	67.2%	−3.5%	.81
KPS score	76.7 ± 10.9	77.9 ± 9.5	75.5 ± 12.1	2.4 ± 1.9	.21
TTR Genotype (top mutations)					
Val30Met	51.1%	54.5%	47.8%	6.8%	
Ser77Tyr	5.3%	3.0%	7.5%	−4.4%	.03[a]
Thr60Ala	13.5%	9.1%	17.9%	−8.8%	
Leu58His	7.5%	3.0%	11.9%	−8.9%	
Other	22.6%	30.3%	14.9%	15.4%	
TTR concentration (g/L)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.0 ± 0.0	.37
Norfolk QoL-DN TQoL score at baseline	47.7 ± 26.1	54.9 ± 27.0	40.6 ± 23.3	14.3 ± 4.4	<.01[a]

Abbreviations: BMI, body mass index; hATTR-CM, hereditary transthyretin amyloidosis with cardiomyopathy; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; KPS, Karnofsky performance status; mBMI, modified body mass index; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; QoL-DN TQoL, Quality of Life–Diabetic Neuropathy total quality-of-life score; SD, standard deviation; TTR, transthyretin.
[a]Statistically significant.

Our study findings build upon earlier results from the subgroup analyses of the original NEURO-TTR trial, as reported by Benson et al.[14] In a pattern consistent with the results of the present analysis, Benson et al[14] found that the impact of inotersen relative to placebo on change of the Norfolk QoL-DN TQoL score at week 66 was greater for patients with Val30Met *TTR* mutation and for patients with no previous treatment with tafamidis or diflunisal. Whereas Benson et al[14] found higher treatment effects for patients with stage 2 disease at baseline, the present analysis showed higher treatment effects for patients with stage 1 disease. This may reflect the multivariate nature of the present analysis, which used a systematic approach to conduct an overall evaluation, whereas the previously performed subgroup analyses by Benson et al[14] were descriptive and univariate. In the study by Benson et al,[14] we also note that the treatment-by-subgroup interaction effects for TTR mutation, disease status, and previous treatment did not attain statistical significance, which likely reflects an insufficient power to detect such effects due to the smaller sample size.

Given the large number of genetic variants associated with ATTRv-PN (more than 140 mutations identified worldwide[7,46]), clinicians have already proposed an individualized approach to care dependent on the specific *TTR* mutation involved.[25] However, symptoms are highly variable, even among patients bearing the same mutation (eg, Val30Met carriers), which speaks to the multifactorial nature of ATTRv-PN.[2,25] Thus, the identification of optimal subgroups in our study may help to further refine individualized treatment decisions and manage patient expectations regarding treatment outcomes. For example, the non-Val30Met mutations, such as Ser77Tyr and Thr60Ala, were associated with a lower inotersen benefit relative to

Val30Met, although the patient counts for each mutation in the analysis sample were too small to draw definitive conclusions. More research is warranted to confirm these findings and to further investigate any mechanisms responsible for the differences in benefit across different phenotypes.

The present study detected a more favorable benefit from inotersen among younger patients with less advanced disease. These findings are consistent with earlier evidence showing that older age at disease onset or treatment initiation and poor clinical status at baseline are key predictors of treatment response in ATTRv-PN, with more pronounced benefits observed among patients who initiate treatment early.[18,39,47] Our findings are particularly relevant given early data on the long-term impact of inotersen on HRQOL in patients with ATTRv-PN enrolled in the ongoing open-label extension study of the NEURO-TTR trial.[46,48] Although inotersen was generally associated with long-term disease stabilization at up to 3 years of follow-up, patients with early initiation showed greater improvements in Norfolk QoL-DN scores over time compared with those with delayed initiation.[46,48] The results of the present study and its open-label extension underscore the need for early diagnosis and early treatment initiation to maximize the benefits of inotersen among these patients.

Research into the domain-specific HRQL benefits of inotersen among patients with hATTR-PN may help to provide additional context to the findings of the NEURO TTR trial. In one exploratory post hoc analysis of the trial data,[49] patients treated with inotersen were found to have preserved or improved scores on specific domains of the Norfolk QoL-DN at 66 weeks relative to baseline, whereas a worsening of mean scores was observed for patients in the placebo arm. In particular, a statistically significant advantage of inotersen over placebo was obtained for the activities of daily living domain, large-fiber/physical functioning domain, and symptoms domain. In the future, the identification of potential subgroups with the greatest benefits on specific domains of the Norfolk QoL-DN may help to further refine individualized treatment decisions for patients with hATTR-PN.

The individualized medicine approach used in our study allowed for the evaluation of multiple patient characteristics simultaneously when defining subgroups, while protecting the estimation from the impacts of post data decisionmaking.[30] Nonetheless, our findings should be considered within the context of certain limitations. In particular, the subgroup analyses should be interpreted with caution given that NEURO-TTR was not designed to discover or confirm subgroup effects and therefore not powered for such subanalyses. Furthermore, the smaller sample sizes may have limited the precision of this analysis, resulting in a potential misestimation of the impact of certain predictors. Further research is warranted to validate the predictors of inotersen benefit identified in this study among other populations and in real-world settings.

5 | CONCLUSIONS

In this study we have identified distinct subgroups of ATTRv-PN patients who were likely to experience the greatest near-term benefits from inotersen relative to placebo, as measured by changes on the Norfolk QoL-DN TQoL instrument. These results underscore the need for early diagnosis and treatment initiation, especially among severely affected patients in early stages of ATTRv-PN, to maximize the benefits of inotersen. Furthermore, the identification of optimal subgroups in the present study may help to inform individualized treatment decisions and manage patient expectations regarding treatment outcomes.

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CONFLICT OF INTEREST

M.V.L., D.B., and A.B. are current or former employees of Ionis Pharmaceuticals/Akcea Therapeutics, and own stock the company. C.K. reports consulting/educational activities for Ionis Pharmaceuticals/Akcea Therapeutics, Alexion, Alnylam, Argenx, Biogen, CSL Behring, Medscape, and Sanofi Genzyme, and has received research grants from Sanofi Genzyme and Akcea Therapeutics. J.S., M.Y., N.D., J.J.Z., and A.G. are employees of Analysis Group, a consulting firm that received payment from Ionis Pharmaceuticals/Akcea Therapeutics for the conduct of this study.

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.

DATA AVAILABILITY STATEMENT

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

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