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CLINICAL RESEARCH ARTICLE

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Neuropathy symptom and change: Inotersen treatment of hereditary transthyretin amyloidosis

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Abstract

Introduction: Hereditary transthyretin-mediated amyloidosis (hATTR) manifests as multisystem dysfunction, including progressive polyneuropathy. Inotersen, an antisense oligonucleotide, improved the course of neuropathic impairment in patients with hATTR in the pivotal NEURO-TTR study (NCT01737398). To determine inotersen's impact on symptoms and patients' neuropathy experience, we performed a post hoc analysis of the Neuropathy Symptoms and Change (NSC) score.

Abbreviations: hATTR, hereditary transthyretin-mediated amyloidosis; HRDB, heart rate during deep breathing; LSM, least-squares mean; mNIS+7, modified Neuropathy Impairment Score +7 neurophysiologic tests; NIS, Neuropathy Impairment Score; Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy questionnaire; NSC, Neuropathy Symptoms and Change; PND, polyneuropathy disability; TTR, transthyretin.

Methods: Stage 1 or 2 hATTR patients were randomized to receive weekly subcutaneous inotersen or placebo for 65 weeks. NSC score was assessed at baseline and 35 and 66 weeks.

Results: At 66 weeks, inotersen-treated patients had symptom stabilization as compared with worsening in patients receiving placebo, based on total NSC score. There were also improvements in the subdomains of muscle weakness, sensory, pain, and autonomic symptoms, and for various individual items.

Discussion: Inotersen treatment stabilized neuropathy symptoms, including autonomic symptoms, in patients with hATTR according to NSC score. Thus, the NSC may be an effective measure to assess neuropathy progression and patients' neuropathy experience in clinical practice.

KEYWORDS

amyloidosis, hATTR, inotersen, Neuropathy Symptoms and Change, transthyretin

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1 | INTRODUCTION

Hereditary transthyretin-mediated amyloidosis (hATTR) is a rare, progressive, and fatal disease that results in the buildup of misfolded transthyretin (TTR) protein in major organ systems, ultimately leading to multisystem dysfunction and major organ failure.[1] Hereditary ATTR is an autosomal-dominant disease most frequently caused by single nucleotide substitutions in the *TTR* gene.[2] Prominent disease manifestations include polyneuropathy and cardiomyopathy, as well as ocular and renal symptoms.[3] The neuropathic manifestations are typically progressive length-dependent sensorimotor and autonomic polyneuropathies, but, due to nonspecific presentation and heterogeneity, diagnosis can be difficult.

Inotersen is a *TTR*-directed antisense oligonucleotide that promotes degradation of the *TTR* mRNA by sequence-specific formation of a substrate for RNase H1 to prevent the production or translation of the TTR protein.[4] In a pivotal study involving patients with hATTR with polyneuropathy (NEURO-TTR; NCT01737398, ClinicalTrials.gov),[5] treatment with inotersen resulted in significant benefit compared with placebo in the coprimary endpoints of the modified Neuropathy Impairment Score +7 neurophysiologic tests (mNIS+7) and the Norfolk Quality of Life–Diabetic Neuropathy questionnaire (Norfolk QoL-DN).

The Neuropathy Impairment Score (NIS) is a quantitative score of motor, sensory, and reflex function as judged by the clinician.[6] The mNIS+7, a primary endpoint in NEURO-TTR, incorporates additions to the NIS that comprise a greater sensory component and assessment of both large and small nerve fiber function.[7] In NEURO-TTR, all components of the mNIS+7 demonstrated significant therapeutic benefit compared with placebo, except for heart rate during deep breathing (HRDB) and touch-pressure tests.[5] Although the mNIS+7 provides assessments on neuropathic impairments, it is still critical to assess symptoms to determine whether improvements in impairments correlate with improvements in symptom severity and, in turn, quality of life.

The Neuropathy Symptoms and Change (NSC) score is a neurologist-administered, patient-answered questionnaire that quantifies the type, distribution, and severity of muscle weakness, sensory symptoms, pain symptoms, and autonomic symptoms, and it was used as an exploratory endpoint in the NEURO-TTR trial.[8]

Herein we evaluate the impact of inotersen treatment on NSC scores in patients with hATTR with polyneuropathy from the NEURO-TTR trial and evaluate the NSC and its subdomains for their utility in detecting a significant effect of inotersen treatment compared with placebo.

2 | METHODS

2.1 | Study design

Details of the methodology and study design of NEURO-TTR have been reported previously.[5] Briefly, NEURO-TTR was a randomized, double-blind, pivotal trial (NCT01737398, ClinicalTrials.gov),[5] in which patients were randomly assigned 2:1 to receive 300 mg/week of subcutaneous doses of inotersen or placebo for 65 weeks.

The trial was conducted in 24 centers in 10 countries (Argentina, Brazil, France, Germany, Italy, New Zealand, Portugal, Spain, United Kingdom, and United States). All patients provided written informed

consent, and the study was approved by the institutional review boards or ethics committees of all institutions and conducted in full accordance with the Declaration of Helsinki and the International Committee on Harmonization Good Clinical Practice guidelines.

2.2 | Participants

Eligible patients were 18 to 82 years of age and had a diagnosis of stage 1 or 2 hATTR with polyneuropathy, an NIS of 10 to 130 points, and documented amyloid deposits, as determined by biopsy and confirmed genetic mutation.

2.3 | Outcomes

The NSC score was an exploratory endpoint in the NEURO-TTR trial that was assessed in tandem with the primary study endpoints, mNIS +7, and Norfolk QoL-DN, at baseline, week 35 (8 months), and week 66 (15 months).

The NSC assessment is a 38-item patient questionnaire administered by a trained neuromuscular physician that explores various neuropathy symptoms in three broad categories: muscle weakness, sensation, and autonomic.[8] The questionnaire suggests specific wording of questions, which are available in more than a dozen languages, but allows for informed physician interpretation of responses. The NSC score comprises the following subdomains: muscle weakness: head and chest (items 1-9), upper limb (items 10-15), and lower limb (items 16-19); sensation: sensory loss (items 20-22), positive neuropathic sensory symptoms (items 23-29), and positive pain symptoms (items 25-29); and autonomic (items 30-38). The NSC score is measured in two ways. The first is change in severity based on serial assessment of symptom severity graded at scheduled visits (ie, NSC symptom severity score). The total NSC symptom severity score ranges from a minimum of 0 to a maximum of 114 for men and 108 for women (two items in the questionnaire are related to sexual dysfunction in men and do not apply to women). If a symptom is not present, it is assigned a score of 0. If a symptom is present, its severity is scored as 1 (mild), 2 (moderate), or 3 (severe). Higher scores indicate *worse* symptom severity; therefore, a negative value in change from baseline indicates an improvement in symptom severity progression. The second way the NSC score is measured is change based on patient recall of present symptoms compared with earlier assessments (ie, NSC change score). Total NSC change score ranges from −114 to 114 for men and −108 to 108 for women; each item was scored as follows: same = 0; better = 1, 2, or 3; and worse = −1, −2, or −3. For the NSC change score, higher, more positive scores indicate greater improvement, whereas lower, more negative scores indicate greater worsening compared with baseline. Note that this scoring method is distinguished from the NSC symptoms severity score in terms of scoring symptom worsening and improvement. We report the NSC change score results as percentage of patients who stabilized or improved (scored ≥0) and patients who worsened (scored <0) based on the median change of the specified items within the total NSC score and each subdomain.

A single study investigator at each study site scored each questionnaire for the same patients over time to maintain consistent assignment of severity score. Importantly, the questionnaire was not validated in each country; however, the questionnaire was translated to each country's primary language and confirmed by experts in those countries to convey the same meaning as the English version. Investigators underwent consensus training for use of the NSC assessment tool. Previous studies have demonstrated that the use of a consensus pretrial process for the assessment of unequivocally abnormal signs and symptoms significantly reduced the variability and improved the accuracy of diagnosing diabetic sensorimotor polyneuropathy compared with assessment based on each physician's usual clinical approach and criteria.[9,10] Investigators who scored the NSC test also performed other neuropathic assessments but did not summate scoring for those assessments and, on subsequent visits, did not review previous results. Thus, the investigator was only partially masked to the overall neuropathic score of impairments.

2.4 | Statistics

Post hoc analyses were done without data imputation to accommodate the exploratory nature of the assessments, unless otherwise specified in the NEURO-TTR statistical analysis plan.[5] The analyses were based on a mixed-effects model with repeated measures, with fixed categorical effects for treatment, time, treatment-by-time interaction, and each of the three randomization stratification factors, and

TABLE 1 Demographics and baseline characteristics of the full analysis set*

Characteristic	Placebo (n = 59)	Inotersen (n = 106)	Total (N = 165)
Age, years	59.4 (14.1)	59.6 (12.4)	59.5 (13.0)
Male	41 (69.5)	75 (70.8)	116 (70.3)
Disease stage 1	42 (71.2)	71 (67.0)	113 (68.5)
Disease stage 2	17 (28.8)	35 (33.0)	52 (31.5)
mNIS+7 composite score	74.1 (39.0)	79.4 (37.5)	77.5 (38.0)
Total NSC score	11.6 (5.4)	12.4 (5.0)	
NSC symptom severity score	22.9 (12.7)	24.9 (13.4)	
PND score			
I	23 (39.0)	31 (29.2)	54 (32.7)
II	19 (32.2)	40 (37.7)	59 (35.8)
III	14 (23.7)	29 (27.4)	43 (26.1)
IV	3 (5.1)	6 (5.7)	9 (5.5)
Duration of disease from diagnosis, months	39.8 (40.5)	43.5 (52.3)	42.1 (48.3)

*Data expressed as mean (standard deviation) or as number (%).
Abbreviations: mNIS+7, modified Neuropathy Impairment Scale +7; NSC, Neuropathy Symptoms and Change; PND, polyneuropathy disability.

fixed covariates for the baseline value and the baseline-by-time interaction. Outcomes are presented for patients in the full analysis set, which included all randomized participants who received at least one dose of study drug and who had a baseline and at least one posttbaseline assessment for the coprimary endpoints. Statistical significance was evaluated using a two-sided $\alpha = 0.05$.

3 | RESULTS

3.1 | Patient population

One hundred seventy-two patients received at least one dose of study drug, of whom 165 were included in the full analysis set. Among these, 106 patients received inotersen 300 mg and 59 patients received placebo. Demographic characteristics were well balanced between the inotersen and placebo groups (Table 1). At baseline, the total NSC score and NSC symptom severity score were similar in patients receiving inotersen and placebo (Table 1). A higher proportion of patients in the placebo group compared with the inotersen group were taking the analgesics pregabalin or gabapentin during treatment (35.6% [n = 21 of 59] vs 21.7% [n = 23 of 106]).

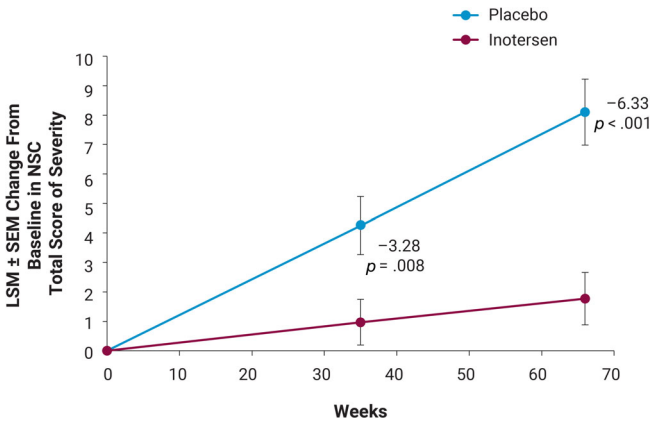

FIGURE 1 Change from baseline in LSM total NSC symptom severity. LSM, least-squares mean; NSC, Neuropathy Symptoms and Change; SEM, standard error of the mean [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | NSC symptom severity score

The inotersen group experienced less symptom worsening compared with the placebo group at 35 weeks ($P = .008$) and 66 weeks ($P < .001$) (Figure 1). Less symptom worsening in the inotersen group compared with the placebo group was also observed in the NSC subdomains of weakness, sensory symptoms, neuropathic sensory symptoms, pain symptoms, and autonomic symptoms (Table 2). The subdomain score of decreased sensation sensory symptoms was not different between the inotersen and placebo groups (Table 2).

For 10 individual items in the NSC questionnaire, the inotersen group showed less symptom worsening compared with the placebo group at week 66 (see Table S1 online).

3.3 | NSC change score

Decreases from baseline in total NSC change score, indicating disease progression as reflected by worsening of patient symptoms, were lower in the inotersen group vs the placebo group at 66 weeks (least-squares mean [LSM] difference, 10.5; 95% confidence interval [CI], 5.5 to 15.6; $P < .001$). In addition, less disease progression ($P < .05$) was observed for the inotersen group compared with the placebo group in each of the NSC subdomain scores except weakness of head and chest, which showed no difference in disease progression between placebo and inotersen. A greater percentage of patients receiving inotersen compared with placebo had improvement or no change of symptoms when assessed by the median change of the specified items in the total NSC change score and in all subdomains except head and chest at week 66 (Figure 2).

TABLE 2 Difference in the LSM change from baseline between inotersen and placebo in total NSC symptom severity score and subdomain scores at 66 weeks

Total score and subdomain	Difference in LSM (inotersen − placebo)	95% CI	*P* value
Total score (items 1-38)	−6.33	−9.12 to −3.55	<.001
Weakness (items 1-19)	−3.07	−4.43 to −1.72	<.001
Weakness in upper limb and in lower limb (items 10-19)	−2.82	−4.04 to −1.60	<.001
Weakness in upper limb (items 10-15)	−1.74	−2.58 to −0.90	<.001
Weakness in lower limb (items 16-19)	−1.10	−1.74 to −0.46	<.001
Sensory symptoms (items 20-29)	−1.90	−3.21 to −0.59	.005
Sensory symptoms, decreased sensation (items 20-22)	−0.04	−0.57 to 0.49	.885
Positive neuropathic sensory symptoms (items 23-29)	−1.88	−2.95 to −0.81	<.001
Positive pain symptoms (items 25-29)	−1.59	−2.37 to −0.81	<.001
Autonomic symptoms (items 30-38)	−1.36	−2.36 to −0.36	.008

Abbreviations: CI, confidence interval; LSM, least-squares mean; NSC, Neuropathy Symptoms and Change.

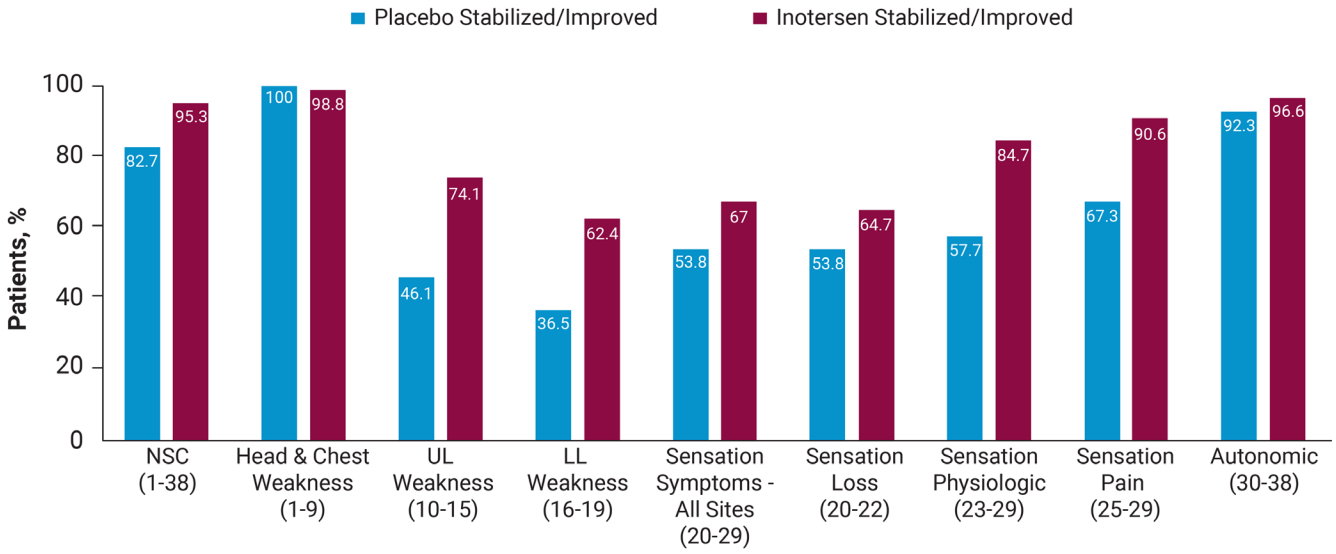

FIGURE 2 Percentage of patients with stabilized/improved or worsening symptoms at week 66. Numbers in parentheses correspond to the items in the NSC assessment pertaining to that subdomain. The results are based on the median change of the specified items within each subdomain. LL, lower limb; NSC, Neuropathy Symptoms and Change; UL, upper limb [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In our analysis of the total NSC score, treatment with inotersen resulted in stabilized symptom severity compared with placebo in all subdomains except for sensory loss.

The NSC assessment also demonstrated that treatment with inotersen had an effect on upper limb and lower limb weakness compared with placebo. Individual items of these subdomains (items 10-13, 16, and 18) showed a difference between inotersen and placebo. Consistent with these results, inotersen reduced progression of the NIS-weakness subcomponent in NEURO-TTR.[5]

Neuropathic sensory symptoms, especially those related to pain, can contribute to poor quality of life.[11,12] Inotersen treatment also showed benefit relative to placebo in the severity of positive neuropathic sensory and positive pain symptom subdomain scores of the NSC assessment; these findings are consistent with results from the sensory components of the mNIS+7 (NIS-sensation and heat-pain).[5] The individual items related to this subdomain (items 25-28) each showed differences between inotersen and placebo. Note that items 13 and 25 to 28 all demonstrated a reduction at week 66 from baseline, indicating improvement in these items, whereas the placebo group showed worsening from baseline at week 66. This suggests that inotersen may not only slow symptom severity progression but can also improve and alleviate the baseline severity of some symptoms. Because inotersen treatment showed benefit in slowing the progression of overall muscle weakness, pain, and neuropathic sensory symptoms, NSC assessment seems to adequately detect changes in these critical subdomains.

The NSC subdomain of sensory loss did not show a difference for change in severity of symptoms between patients receiving inotersen and those receiving placebo. However, differences between inotersen and placebo were shown in NIS-sensation and heat-pain, which are other components of the mNIS+7 that describe sensory loss symptoms, from baseline to week 66. It is noteworthy that positive sensory symptoms (prickling and pain) showed an effect in favor of inotersen, whereas negative sensory symptoms (loss of feeling) did not. One may surmise that the positive symptoms were more troubling and noticeable to the patients with hATTR.

In the NEURO-TTR study, no difference was observed between inotersen and placebo in the HRDB test, which may suggest little effect on autonomic neuropathy. This result, however, is likely attributable to many patients (41.2% of inotersen patients and 36.5% of placebo patients) in the NEURO-TTR trial not having HRDB data available for analysis due to the presence of active pacing or atrial fibrillation, which is common in this population. In this post hoc analysis, treatment with inotersen resulted in a significant benefit compared with placebo in the NSC autonomic subdomain. These results suggest that inotersen may prevent worsening of autonomic symptoms and that the NSC may be an effective measure of autonomic symptom severity in hATTR. In addition, for NSC change score, more patients in the inotersen group reported stabilization or improvement in symptoms at week 66 compared with those in the placebo group in all NSC subdomains. Of the placebo group, 82.7% had no change or improvement to their NSC score when assessed by the median change of all items. This proportion is high likely because of the relatively short-term nature of the NEURO-TTR study, as we would not expect a major change in symptoms over a period of 18 months. This result seems consistent with the natural history of the disease. Overall, the NSC score data indicate that the effect of inotersen on nerve impairment has a beneficial impact on symptomatic progression, providing clinical impact to the mNIS+7 findings.

Another advantage of the NSC questionnaire is how quickly the assessment can be performed compared with other very time-consuming conduction studies of the mNIS+7. If the patient is essentially

asymptomatic, the questionnaire of 38 items can be done in 10 to 15 minutes by an expert. On the other hand, if the patient has severe symptoms, it may take 30 to 45 minutes or longer. This makes the NSC test a more useful tool to track disease progression in real-world clinical practice compared with the mNIS+7. In addition, although other hATTR disease staging systems, such as those described by Coutinho et al and Yamamoto et al, can track disease progression, they are somewhat limited, as the staging focuses on difficulty of ambulation and largely ignores other relevant neuropathy symptoms that can evolve in hATTR with polyneuropathy.[13,14] The NSC questionnaire can track progression of these other polyneuropathy symptoms.

Possible limitations of the NSC questionnaire include patient-recall bias and that patients with hATTR can experience varying emotional states, including depressive moments or moments of denial, which can affect responses to the questionnaire. Note that the NEURO-TTR trial included various other quality-of-life measures, such as the Norfolk QoL-DN and the 36-item Short Form questionnaire, the latter of which includes various other symptoms or factors relevant to hATTR with polyneuropathy, such as global well-being. These factors may not necessarily be captured in the NSC questionnaire, which focuses on neuropathy-related symptom severity. Further analyses of the NSC tool are needed to provide a critical understanding of its applicability in the setting of hATTR with polyneuropathy, along with its utility for future studies and in real-world practice.

Overall, treatment with inotersen has been shown to be effective in the patients' experience of their symptoms. The NSC questionnaire showed significant differences in favor of inotersen for all subdomains except sensory loss, which confirms the efficacy of inotersen in patients with hATTR on various polyneuropathy endpoints. Use of the NSC also emphasizes the patients' experience of their disease, which can be valuable endpoints in addition to the investigators' observations on examination and testing via the mNIS+7. The results of this analysis show that the NSC questionnaire is an excellent tool for monitoring the progression of many specific polyneuropathy symptoms seen in patients with hATTR.

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CONFLICT OF INTEREST

P.J.B.D. has received honoraria/consultancy fees from Akcea. T.C. has received financial support to attend scientific meetings from Pfizer, Alnylam, and Biogen. M.W.C. has received honoraria/consultancy fees from NHI, Prothena, FoldRx, Ionis, Pfizer, Alnylam, PTC Therapeutics, and Genzyme for travel expenses related to presentations at medical meetings and for acting as a principal investigator in clinical trials. T.H.B. is on advisory boards for Akcea, Pfizer, and Alnylam; is a study investigator for Ionis and Alnylam; is a speaker for Alnylam; and has received speaker honoraria from Akcea. S.K. has received honoraria from Akcea and Alnylam. C.K. has served as a paid consultant for Akcea, Alnylam, Alexion, Biogen, CSL Behring, Cytokinetics, and Genzyme. J.L.B. has received honoraria from Ionis and Alnylam, and is a study investigator for Ionis, Alnylam, and Pfizer. M.J.P. has received honoraria from Pfizer and Alnylam. J.C.K. is a subinvestigator at the NEURO-TTR treatment trial site and has received honoraria/consultancy fees from Akcea. J.F.W. is a subinvestigator at the NEURO-TTR treatment trial site and has received consultancy fees from Ionis. W.J.L. has received grant/research support from Alnylam. M.L.M. has received research support from Ionis and Alnylam and has served as a consultant for Ionis. E.J.A. has received consultancy fees from Akcea. B.F.B. and S.W.J. are employees of Ionis. S.G. is an employee of Aurora Bio and former employee of Akcea. M.P. is an employee and shareholder of Akcea. P.J.D. has received financial support for the training of investigators for the conduct of therapeutic trials in hATTR with polyneuropathy from Ionis and Alnylam; he is also a consultant for Ionis and Alnylam.

ETHICAL PUBLICATION 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.

POTENTIAL COVER ART

Images of a longitudinal paraffin section stained with Congo Red from a sural nerve biopsy showing transthyretin amyloid deposition (L, regular light; R, polarized light). Consequent peripheral nerve function and damage in patients with hATTR assessed by two principal methods in the clinical investigation of inotersen. For details, see Dyck et al: mNIS +7 and Lower Limb Function in Inotersen Treatment of hATTR, pages #-#; and Dyck et al: Neuropathy Symptom and Change: Inotersen Treatment of Hereditary Transthyretin Amyloidosis, pages #-#.

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SUPPORTING INFORMATION

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

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