

# RNAi Efficacy in Large and Small Fiber-Predominant Polyneuropathy of Hereditary Transthyretin Amyloidosis: HELIOS-A Post-Hoc Analysis

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## Conclusions

- RNAi therapeutics vutrisiran and patisiran improved or prevented worsening of mNIS+7 regardless of baseline NCS sum scores
- In patients with early disease and minimal NCS abnormalities (NCS <2, less large-fiber involvement), patients had greater improvement in mNIS+7, primarily driven by QST. This finding in patients with less large-fiber involvement suggests predominant effects on small fibers
- In later disease (NCS ≥2), RNAi therapeutics address both fiber types, evidenced by effects on mNIS+7 and greater reductions in NfL, a marker for large-fiber neuropathy, compared with the NCS <2 group
- More patients in the baseline NCS <2 group showed potential disease reversal, supporting initiation of RNAi therapeutics as early as possible in the hATTR-PN disease course, reinforcing the importance of early diagnosis and treatment

**Key takeaway**

RNAi therapeutics vutrisiran and patisiran are effective for patients with hATTR-PN regardless of the degree of baseline nerve conduction study abnormalities

## Introduction

### hATTR-PN

- Hereditary transthyretin amyloidosis (hATTR) is a rapidly progressive, debilitating, fatal disease caused by variants of the *TTR* gene<sup>1-3</sup>
- Accumulation of misfolded TTR as amyloid deposits in the nerves, cardiac tissue, and other systems can manifest as polyneuropathy, cardiomyopathy, or a mixed phenotype<sup>1-3</sup>
- Polyneuropathy in patients with hATTR (hATTR-PN) is associated with various sensory, motor and autonomic nerve alterations.<sup>3</sup> It can involve both small and large nerve fibers, with small fibers often affected first<sup>2,4,5</sup>
- Large-fiber neuropathy may be diagnosed via clinical history, examination (e.g., motor weakness, abnormal vibratory sensations, and proprioception impairment) and/or nerve conduction study (NCS)<sup>2,4,5</sup>

### Vutrisiran and Patisiran

- The RNAi therapeutics vutrisiran and patisiran decrease hepatic TTR synthesis and are approved for the treatment of hATTR-PN based on data from the phase 3 HELIOS-A (NCT03759379) and APOLLO (NCT01960348) studies, respectively<sup>6-9</sup>
- Vutrisiran and patisiran demonstrated robust treatment effects in patients with hATTR-PN across a broad range of disease severities, including those with mild disease<sup>10,11</sup>
- The outcomes of patients with varying degrees of NCS abnormalities at baseline, which may reflect disease stage and degree of large-fiber involvement, have not been examined independently

### Objective

- This post-hoc analysis of HELIOS-A evaluated the efficacy of RNAi therapeutics in patients with hATTR-PN according to baseline NCS sum score (<2 vs ≥2) reflecting less vs more large-fiber involvement, respectively

## Methods

- HELIOS-A was an international, multicenter, open-label, randomized, phase 3 study in patients with hATTR-PN in which patients were randomized 3:1 to receive vutrisiran (25 mg SC Q3M) or patisiran (0.3 mg/kg IV Q3W) for 18 months<sup>11</sup>
- In this post-hoc analysis, treatment effects at Month 18 were compared between patients with a baseline NCS sum score <2 vs ≥2
- NCS sum score <2 and NCS sum score ≥2 were calculated based on the sural SNAP, ulnar SNAP, ulnar CMAP, tibial CMAP, and peroneal CMAP amplitudes (range 0–2 for each component [0=normal, 1=mildly reduced, 2=very reduced], maximum score of 10)<sup>12</sup>

## Results

**Table 1. Demographics and Baseline Characteristics by Baseline NCS Sum Score Subgroup**

	NCS Sum Score <2 (n=37)	NCS Sum Score ≥2 (n=127)
<b>Age, years, median (range)</b>	60.0 (37.0–80.0)	60.0 (26.0–85.0)
<b>Male, n (%)</b>	18 (48.6)	88 (69.3)
<b>Race, n (%)</b>		
Asian	4 (10.8)	25 (19.7)
Black or African American	1 (2.7)	7 (5.5)
White	26 (70.3)	89 (70.1)
Multiple	1 (2.7)	0
Other	5 (13.5)	6 (4.7)
<b>Time since hATTR diagnosis, years, median (range)</b>	2.4 (0.1–13.4)	2.2 (0.0–15.3)
<b>Genotype, n (%)</b>		
V30M	13 (35.1)	61 (48.0)
Non-V30M	24 (64.9)	66 (52.0)
<b>BMI, kg/m<sup>2</sup>, mean (SD)</b>	27.0 (4.4)	23.8 (4.9)
<b>mNIS+7 score, mean (SD)</b>	27.4 (22.9)	69.3 (32.7)
<b>Norfolk QoL-DN score, mean (SD)</b>	33.1 (28.4) <sup>a</sup>	51.2 (25.6)
<b>10-MWT, mean (SD)</b>	1.236 (0.298)	0.940 (0.394)
<b>NfL (pg/mL), mean (SD)</b>	25.9 (30.0)	69.1 (39.9) <sup>b</sup>

<sup>a</sup>n=36; <sup>b</sup>n=110.

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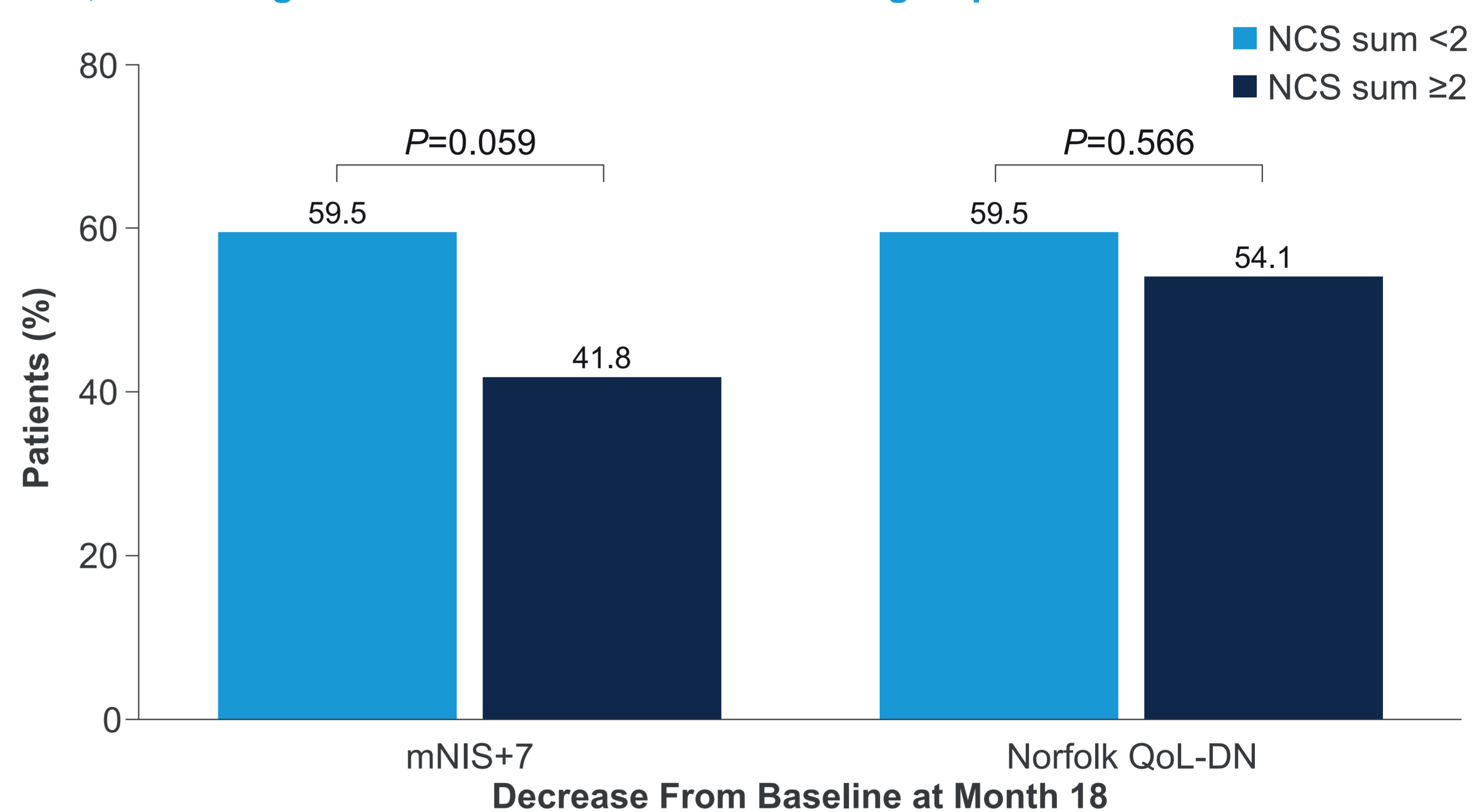
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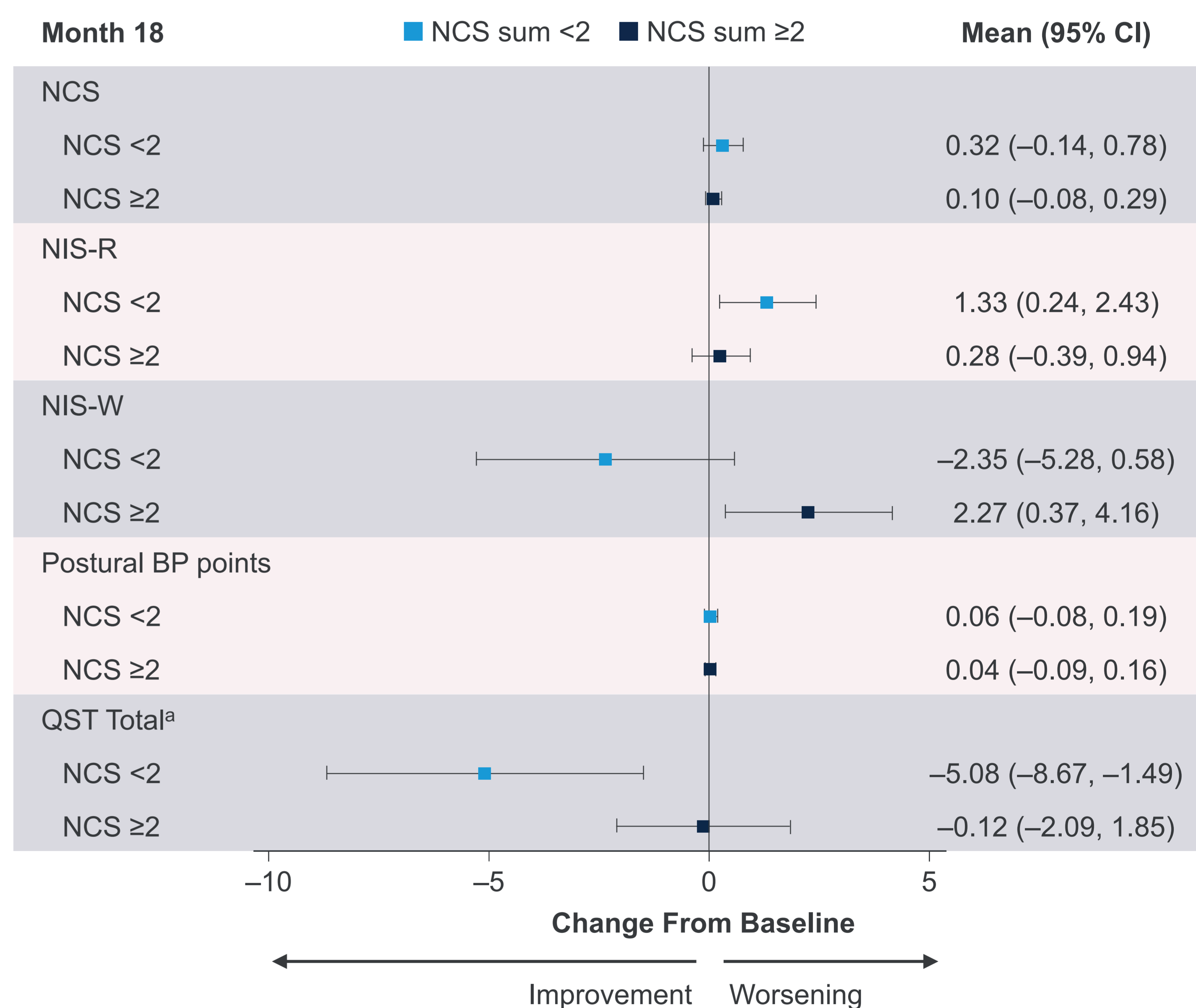
## Results

- At M18 in the overall population, mNIS+7 improved in NCS <2 patients (n=36) vs baseline (mean [SD] change –5.7 [13.1], *P*=0.013) and was maintained in NCS ≥2 patients (n=112; mean [SD] change 2.6 [16.4], *P*=0.102)
  - For reference, in the placebo group of the APOLLO study (n=77), least-squares mean (SE) change from baseline in mNIS+7 at Month 18 was 28 (2.6)<sup>10</sup>
- The efficacy of RNAi therapeutics was generally consistent between patients with high and low baseline NCS across measures of polyneuropathy

**Figure 1. Proportion of Patients With Potential Disease Reversal, Defined as Decrease From Baseline at Month 18 in mNIS+7 Score or in the Norfolk QoL-DN Score, According to Baseline NCS Sum Score Subgroup**



**Figure 2. Forest Plot of Change From Baseline in mNIS+7 Individual Components At Month 18 by Baseline NCS Sum Score Subgroup**



<sup>a</sup>QST measures heat pain and touch pressure from 10 distributed anatomic sites on one side of the body. Scoring is based on point abnormality (<95th=0 point, ≥95th–<99th=1 point, and ≥99th=2 points). The test score is 2 × the total scores for QST of heat pain by body surface area and QST of touch pressure by body surface area. The maximum total score for QST is 80.

**Table 2. Change From Baseline in Norfolk QoL-DN Score, 10-MWT, and NfL Levels at Month 18 by Baseline NCS Sum Score Subgroups**

Mean (SD)	NCS Sum Score <2 (n=37)	NCS Sum Score ≥2 (n=127)
<b>Norfolk QoL-DN score</b>		
n	35	114
Change from baseline	–4.0 (23.0)	–1.3 (19.6)
<i>P</i> value	0.501	
<b>10-MWT speed (m/s)</b>		
n	36	114
Change from baseline	0.026 (0.268)	–0.038 (0.261)
<i>P</i> value	0.204	
<b>NfL (pg/mL)</b>		
n	35	100
Change from baseline	–3.6 (15.3)	–24.6 (34.4)
<i>P</i> value	<0.001	

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**Abbreviations:** 10-MWT, 10-minute walk test; BMI, body mass index; BP, blood pressure; CI, confidence interval; CMAP, compound muscle action potential; hATTR, hereditary transthyretin amyloidosis; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; IV, intravenous; mNIS+7, modified neuropathy impairment score+7; NCS, nerve conduction study; NfL, neurofilament light chain; NIS, neuropathy impairment score; NIS-R, neuropathy impairment score-reflex; NIS-W, neuropathy impairment score-walk; QoL, quality of life; QoL-DN, Quality of Life-Diabetic Neuropathy questionnaire; QST, quantitative sensory testing; Q3M, every three months; Q3W, every three weeks; RNAi, RNA interference; SC, subcutaneous; SD, standard deviation; SNAP, sensory nerve action potential; TTR, transthyretin.