ORIGINAL RESEARCH

Impact of Baseline Neuropathy Severity on Vutrisiran Treatment Response in the Phase 3 HELIOS-A Study

Marco Luigetti [ID] · Dianna Quan · John L. Berk · Isabel Conceição ·

Yohei Misumi · Chi-Chao Chao · Shaun Bender · Emre Aldinc ·

John Vest · David Adams

ABSTRACT

Introduction: Hereditary transthyretin (ATTRv, v for variant) amyloidosis is a rare, progressive, fatal disease with multisystem manifestations, caused by pathogenic variants in the transthyretin (*TTR*) gene. Vutrisiran, an RNA interference therapeutic that results in rapid TTR knockdown, improved neuropathy and quality of life (QOL) versus external placebo in patients with ATTRv amyloidosis with polyneuropathy in the phase 3 HELIOS-A study (NCT03759379). This post hoc analysis evaluates the impact of baseline neuropathy severity on response to vutrisiran treatment.

Methods: Patients were randomized (3:1) to vutrisiran ($n = 122$; 25 mg subcutaneous injection once every 3 months) or patisiran ($n = 42$;

M. Luigetti (✉)
Dipartimento di Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli, 8, 00168 Rome, Italy
e-mail: mluigetti@gmail.com

M. Luigetti
Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy

D. Quan
Department of Neurology, University of Colorado Anschutz, Aurora, CO, USA

J. L. Berk
Boston Medical Center, Boston, MA, USA

I. Conceição
Department of Neurology, CHULN, Hospital Santa Maria and Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

Y. Misumi
Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

C.-C. Chao
Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan

S. Bender · E. Aldinc · J. Vest
Alnylam Pharmaceuticals, Cambridge, MA, USA

D. Adams
Neurology Department, Université Paris-Saclay, U1195, INSERM, AP-HP, CHU Bicêtre, Le Kremlin Bicêtre, France

0.3 mg/kg intravenous infusion once every 3 weeks), which served as a reference group. In this post hoc analysis, patients were grouped into quartiles of increasing baseline Neuropathy Impairment Score (NIS): Quartile (Q)1 $\geq$ 5.0 to $\leq$ 20.5; Q2 > 20.5 to $\leq$ 44.1; Q3 > 44.1 to $\leq$ 73.1; Q4 > 73.1 to $\leq$ 127.0. Mean change from baseline to Month 18 was summarized by quartile for a range of efficacy endpoints.

Results: Across all baseline NIS quartiles, vutrisiran demonstrated benefit versus external placebo in measures of neuropathy severity (modified NIS + 7), QOL (Norfolk Quality of Life-Diabetic Neuropathy), disability (Rasch-built Overall Disability Scale), gait speed (10-m walk test), and nutritional status (modified body mass index). Overall, patients in lower versus higher NIS quartiles (less severe neuropathy) at baseline maintained better scores at Month 18. The external placebo group progressively worsened in all measures at Month 18.

Conclusions: Vutrisiran demonstrated benefit in neurologic function and other key efficacy measures versus external placebo across all four baseline neuropathy severity quartiles. Patients initiating vutrisiran earlier in their disease course retained the highest neurologic function level after 18 months, highlighting the importance of early diagnosis and treatment.

Trial Registration Number: ClinicalTrials.gov: NCT03759379.

Keywords: ATTRv amyloidosis; Baseline NIS quartiles; Disability; Neuropathy severity; Nutritional status; Polyneuropathy; Quality of life; RNA interference; Vutrisiran

Key Summary Points

Why carry out this study?

Hereditary transthyretin (ATTRv, v for variant) amyloidosis, also known as hATTR amyloidosis, is a rare, progressive, and fatal disease, in which continued progression of neuropathy and/or cardiomyopathy leads to debilitating symptoms with increasing severity, impaired physical function, and decline in nutritional status and patients' quality of life (QOL).

To better understand the disease trajectory of ATTRv amyloidosis, this post hoc analysis of the phase 3 HELIOS-A study assessed the response to vutrisiran treatment in measures of neuropathy, physical function, and QOL in patients with various baseline severities of neuropathy, as categorized by Neuropathy Impairment Score (NIS) quartiles.

What was learned from the study?

Vutrisiran provided treatment benefit compared with external placebo across a range of disease-relevant outcomes (neuropathy severity [modified NIS + 7], QOL [Norfolk Quality of Life–Diabetic Neuropathy], disability [Rasch-built Overall Disability Scale], gait speed [10-m walk test], and nutritional status [modified body mass index]) across all baseline NIS quartiles.

Patients initiating vutrisiran earlier in their disease course (i.e., those in the lower NIS quartiles) retained the highest neurologic function level after 18 months.

The findings of this study support the clinical benefit of vutrisiran as an effective treatment that can improve the lives of patients with ATTRv amyloidosis with polyneuropathy, regardless of baseline neuropathy severity, and highlight the importance of early diagnosis and treatment.

INTRODUCTION

Hereditary transthyretin (ATTRv, v for variant) amyloidosis, also known as hATTR amyloidosis, is a rare, progressive, debilitating, and fatal disease caused by variants in the transthyretin (*TTR*) gene [1–4]. Pathogenic *TTR* variants lead to misfolding of TTR proteins, which accumulate as amyloid deposits in multiple organs and tissues [5, 6], including nerves, heart, gastrointestinal tract, and musculoskeletal tissues [1, 2, 4, 7]. As such, ATTRv amyloidosis is a multisystem disease with a heterogeneous clinical presentation typically involving sensory, motor, and autonomic neuropathy, and cardiomyopathy [2, 8–10], with the majority of patients presenting with a mixed phenotype of polyneuropathy and cardiomyopathy [11, 12]. ATTRv amyloidosis has an aggressive course, and disease progression is associated with increased symptom severity, decreased quality of life (QOL), loss of physical function, and death [3, 13, 14]. In untreated patients, prognosis is poor, with a median survival of 4.7 years following diagnosis [15], and a reduced survival of 3.4 years in patients with cardiomyopathy [16].

The natural course of ATTRv amyloidosis highlights the need for early and effective treatment that can minimize the burden of disease and the progressive worsening of QOL and physical function. The rapid progression of the disease when not treated is evident in natural history studies [3, 17, 18] and the placebo arms of pivotal clinical studies in patients with ATTRv amyloidosis [13, 19–22], in which outcomes measures related to neuropathy severity (e.g., modified Neuropathy Impairment Score + 7 [mNIS + 7]), QOL (Norfolk Quality of Life–Diabetic Neuropathy [Norfolk QOL-DN] questionnaire), disability (Rasch-built Overall Disability Scale [R-ODS]), and nutritional status (modified body mass index [mBMI]) steadily deteriorate over time.

Current disease-modifying treatment strategies for ATTRv amyloidosis include those that reduce levels of pathogenic TTR protein by silencing the *TTR* gene (RNA interference [RNAi] therapeutics; antisense oligonucleotides [ASO]), or those that stabilize the TTR tetramer (TTR stabilizers). These strategies have shown different levels of clinical benefit versus placebo in various manifestations in patients with ATTRv amyloidosis [19–21, 23].

The RNAi therapeutic patisiran, approved for treatment of patients with ATTRv amyloidosis with polyneuropathy [24], demonstrated the potential to halt polyneuropathy progression and improve multiple QOL and disability measures compared with placebo at 18 months in the pivotal phase 3 APOLLO study [13, 19]. A post hoc analysis also demonstrated that these improvements or stabilizations in neurologic function and QOL with patisiran versus placebo were evident across a wide range of baseline neuropathy severities [25]. Vutrisiran, another RNAi therapeutic that, like patisiran, acts by reducing the synthesis of both variant and wild-type TTR in the liver, and resulting in rapid knockdown of circulating TTR, has also been approved for the treatment of the polyneuropathy of ATTRv amyloidosis [26]. In the phase 3 HELIOS-A study in patients with ATTRv amyloidosis with polyneuropathy, vutrisiran met the primary endpoint of change from baseline in neuropathy impairment (mNIS + 7) compared with an external placebo group from the APOLLO study, as well as all secondary efficacy endpoints, and demonstrated an acceptable safety profile [27].

To better understand the disease trajectory of ATTRv amyloidosis, following a similar analysis to the aforementioned post hoc analysis of the APOLLO study, we report the efficacy of vutrisiran observed in the HELIOS-A study in patients with various baseline severities of neuropathy (as categorized by Neuropathy Impairment Score [NIS] quartiles).

METHODS

Trial Design

The full methodology and study design details for the HELIOS-A study have been described previously [27]. In summary, the HELIOS-A study was a phase 3, global, randomized, open-label study of patients with ATTRv amyloidosis

with polyneuropathy, and was conducted at 57 sites in 22 countries (NCT03759379). The study protocol and amendments were approved by relevant Institutional Review Boards or Independent Ethics Committees. Written informed consent was obtained from each participant. The study was conducted in accordance with all applicable regulatory requirements, the current guidelines of Good Clinical Practice, and principles originating from the Declaration of Helsinki.

Study Population

Eligible patients in the HELIOS-A study were aged 18–85 years with a documented *TTR* variant and diagnosis of ATTRv amyloidosis, neuropathy (baseline NIS of 5–130), a polyneuropathy disability score of ≤ IIIb, adequate liver and renal function, and a Karnofsky Performance Status (KPS) score of ≥ 60%. Patients who had received previous gene-silencing therapy, those with prior liver transplantation, those who were planned to undergo liver transplantation during the 18-month treatment period, and those with New York Heart Association class > II were excluded. Prior TTR stabilizer use was permitted, although patients were not allowed to use TTR stabilizers during their participation in the study.

Randomization and Treatment

Enrolled patients were randomized in a 3:1 ratio to 18 months of treatment with vutrisiran 25 mg subcutaneously once every 3 months or patisiran 0.3 mg/kg intravenously once every 3 weeks, which served as a reference group. The placebo group of the APOLLO study [19], which had similar eligibility criteria and endpoints to the HELIOS-A study, was used as an external placebo control for the primary endpoint and most secondary and exploratory endpoints.

Assessments

Full details of the primary, secondary, and exploratory efficacy and safety endpoints of the HELIOS-A study have been reported previously [27]. Briefly, the primary endpoint was the change in neuropathy impairment from baseline as measured by mNIS + 7 (range 0–304, with higher scores indicating greater neuropathy impairment) compared with the external placebo group of the APOLLO study at Month 9. mNIS + 7 was also assessed at Month 18 as a secondary endpoint. Here, we evaluate the impact of baseline neuropathy severity, as defined by baseline NIS quartiles, on the efficacy of vutrisiran in multiple outcome measurements such as neuropathy (mNIS + 7), QOL (Norfolk QOL-DN), functional status (R-ODS score), gait speed (10-m walk test [10-MWT]), and nutritional status (mBMI) over 18 months in patients treated with vutrisiran in the HELIOS-A study.

The NIS is a 244-point composite score derived from the assessment of muscle strength, reflexes, and sensation in the upper and lower limbs [28]. The mNIS + 7 score was developed from the NIS assessment and includes seven assessments in addition to the ones included in the NIS, which include five nerve conduction studies, a vibration detection threshold, and postural blood pressure [28]. For both NIS and mNIS + 7, a higher score indicates greater neurologic impairment. The 10-MWT assesses the time needed for a patient to walk 10 m, with longer time taken indicating worse ambulatory function. Norfolk QOL-DN is a 35-item questionnaire comprising five domains: physical functioning/large-fiber neuropathy, symptoms, activities of daily living, small-fiber neuropathy, and autonomic neuropathy (range – 4 to 136, with higher score indicating worse QOL) [29]. R-ODS is a 24-item, patient-reported scale that measures limitations in normal activities of daily living and social participation (range 0–48, with a lower score indicating more disability) [30]. Worse nutritional status is indicated by a lower mBMI score (weight/square of height [kg/m^2] × serum albumin [g/L]). mBMI was chosen instead of BMI as patients with ATTRv amyloidosis may have low serum albumin levels due to malnutrition, leading to fluid retention and edema, which can result in increased weight and normal BMI measurements despite worsening nutritional status.

Statistical Analysis

Full details of the statistical analyses of the HELIOS-A study have been described previously [27]. For this post hoc subgroup analysis, patients from the vutrisiran group in the HELIOS-A study and the placebo group in the APOLLO study (external placebo) were divided into four quartiles based on increasing baseline NIS, from the least severe neuropathy impairment in quartile (Q)1: ≥ 5.0 to ≤ 20.5 ($n = 50$), then Q2: > 20.5 to ≤ 44.1 ($n = 50$) and Q3: > 44.1 to ≤ 73.1 ($n = 50$), to the most severe neuropathy impairment in Q4: > 73.1 to ≤ 127.0 ($n = 49$). Baseline demographics and disease characteristics were summarized by treatment group for each baseline NIS quartile. Data were descriptively summarized for the modified intent-to-treat population (defined as randomized patients who received any dose of study drug) as mean change from baseline at 9 and 18 months for each endpoint in each baseline NIS quartile. 10-MWT was calculated as the mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk.

RESULTS

Baseline Demographic and Disease Characteristics

Baseline characteristics by treatment group and by baseline NIS quartile are reported in Table 1. Baseline polyneuropathy, as assessed by NIS, ranged from 5 to 127 points, reflecting the range of neurologic impairment at baseline in both the HELIOS-A vutrisiran and the APOLLO placebo groups. In both groups, there were comparable proportions of patients in the respective Q2 and Q3 quartiles. In the vutrisiran group, there was a greater proportion of patients in Q1 at baseline, with the lowest proportion of patients in Q4. In contrast, in the external placebo group, the lowest and highest proportion of patients were in Q1 and Q4, respectively.

Median age was comparable between the external placebo and vutrisiran groups within each quartile, with patients in Q1 having a lower median age compared with patients in higher quartiles (Table 1). The patient populations in vutrisiran and external placebo groups were generally comparable within each quartile in terms of mNIS + 7, Norfolk QOL-DN, R-ODS, and mBMI. On the other hand, there were differences in baseline characteristics, including 10-MWT, KPS, percentage of patients with Val30Met TTR variant (V30M)/non-V30M, and percentage of patients meeting the definition of cardiac subpopulation between the treatment groups in some of the quartiles (Table 1).

For the external placebo group, there were treatment discontinuations in all NIS quartiles. Over time, a higher rate of discontinuation was observed in those patients with greater baseline neuropathy severity (3 of 12 patients [25.0%] in Q1 and 13 of 27 patients [48.1%] in Q4 discontinued treatment). For the vutrisiran group, there were no discontinuations in Q1 or Q4, while 2 of 32 (6.3%) patients in Q2 and 4 of 30 (13.3%) patients in Q3 discontinued treatment (Table 2). The reasons for treatment discontinuation across each treatment group and NIS quartile are listed in Table 2.

Polyneuropathy (mNIS + 7) Assessments by Baseline NIS Quartile

Within each baseline NIS quartile, baseline mNIS + 7 scores were generally comparable between the vutrisiran and external placebo groups (Table 1). Vutrisiran demonstrated a beneficial treatment effect on mNIS + 7 across all baseline NIS quartiles, relative to the external placebo group, which was first evident at Month 9 (Fig. 1).

When change in mNIS + 7 score from baseline was evaluated in different baseline NIS quartiles, vutrisiran-treated patients in Q1 and Q2 (i.e., less severe neuropathy at baseline) showed improved polyneuropathy at Months 9 and 18, as demonstrated by a negative mean change in mNIS + 7 score from baseline (Fig. 1). By Month 18, patients in Q3 and Q4 (i.e., more severe neuropathy at baseline) demonstrated modest worsening of polyneuropathy, as evidenced by relatively small increases in mNIS + 7 scores versus baseline. In contrast, across all

Table 1 Baseline demographics and disease characteristics of patients across the NIS quartiles and the mITT population

Characteristic	HELIOS-A Vutrisiran (n = 122)				APOLLO External placebo (n = 77)			
	Q1 ≥ 5.0 to ≤ 20.5 (n = 38)	Q2 > 20.5 to ≤ 44.1 (n = 32)	Q3 > 44.1 to ≤ 73.1 (n = 30)	Q4 > 73.1 to ≤ 127.0 (n = 22)	Q1 ≥ 5.0 to ≤ 20.5 (n = 12)	Q2 > 20.5 to ≤ 44.1 (n = 18)	Q3 > 44.1 to ≤ 73.1 (n = 20)	Q4 > 73.1 to ≤ 127.0 (n = 27)
Age, median (range), years	54.5 (31–73)	62.5 (31–78)	63.5 (26–85)	64.0 (44–81)	53.0 (36–75)	64.0 (38–80)	62.5 (34–77)	66.0 (43–77)
Male, n (%)	18 (47.4)	24 (75.0)	20 (66.7)	17 (77.3)	6 (50.0)	13 (72.2)	16 (80.0)	23 (85.2)
Time since ATTRv diagnosis, mean (SD), years	4.2 (4.1)	2.9 (3.8)	3.4 (3.5)	2.6 (3.0)	3.8 (4.5)	1.9 (2.4)	2.5 (2.6)	2.7 (3.6)
TTR genotype, n (%)								
V30M	18 (47.4)	10 (31.3)	16 (53.3)	10 (45.5)	8 (66.7)	8 (44.4)	10 (50.0)	14 (51.9)
Early onset (< 50 years of age at onset)	10 (26.3)	6 (18.8)	7 (23.3)	2 (9.1)	4 (33.3)	2 (11.1)	1 (5.0)	3 (11.1)
Non-V30M[a]	20 (52.6)	22 (68.8)	14 (46.7)	12 (54.5)	4 (33.3)	10 (55.6)	10 (50.0)	13 (48.1)
Previous TTR stabilizer, n (%)	24 (63.2)	18 (56.3)	16 (53.3)	17 (77.3)	5 (41.7)	9 (50.0)	16 (80.0)	11 (40.7)
Karnofsky performance status, n (%)								
60	0	0	6 (20.0)	11 (50.0)	1 (8.3)	1 (5.6)	4 (20.0)	16 (59.3)
70–80	18 (47.4)	23 (71.9)	22 (73.3)	10 (45.5)	10 (83.3)	12 (66.7)	14 (70.0)	9 (33.3)
90–100	20 (52.6)	9 (28.1)	2 (6.7)	1 (4.5)	1 (8.3)	5 (27.8)	2 (10.0)	2 (7.4)
Cardiac subpopulation[b], n (%)	5 (13.2)	9 (28.1)	12 (40.0)	14 (63.6)	0	8 (44.4)	11 (55.0)	17 (63.0)
mNIS + 7, mean (SE)	25.4 (2.9)	48.5 (3.4)	85.9 (3.6)	104.2 (4.6)	26.3 (3.3)	47.8 (3.4)	77.2 (4.7)	112.1 (4.1)
Norfolk QOL-DN, mean (SE)	29.7 (3.5)[c]	42.7 (4.1)	58.0 (3.6)	68.1 (5.5)	34.9 (4.0)	41.1 (5.0)	63.5 (4.7)	68.9 (4.2)[d]
10-MWT, mean (SE)	1.25 (0.04)	1.24 (0.05)	0.79 (0.05)	0.54 (0.05)	1.05 (0.07)	0.95 (0.06)	0.80 (0.05)	0.56 (0.05)

Table 1 continued

Characteristic	HELIOS-A Vutrisiran (n = 122)				APOLLO External placebo (n = 77)			
	Q1 ≥ 5.0 to ≤ 20.5 (n = 38)	Q2 > 20.5 to ≤ 44.1 (n = 32)	Q3 > 44.1 to ≤ 73.1 (n = 30)	Q4 > 73.1 to ≤ 127.0 (n = 22)	Q1 ≥ 5.0 to ≤ 20.5 (n = 12)	Q2 > 20.5 to ≤ 44.1 (n = 18)	Q3 > 44.1 to ≤ 73.1 (n = 20)	Q4 > 73.1 to ≤ 127.0 (n = 27)
R-ODS, mean (SE)	41.6 (1.1)	38.5 (1.2)	31.2 (1.4)	18.7 (1.7)	41.3 (2.0)	35.2 (1.7)	31.0 (1.7)	19.7 (1.5)[d]
mBMI, mean (SE)	1171.4 (39.2)	1089.8 (35.8)	927.7 (31.0)	990.2 (51.3)	1098.6 (66.1)	1004.2 (46.4)	899.9 (52.5)	998.8 (35.7)

10-MWT 10-m walk test, ATTRv hereditary transthyretin (v for variant), mBMI modified body mass index, mITT modified intent-to-treat, mNIS + 7 modified Neuropathy Impairment Score + 7, NIS Neuropathy Impairment Score, Norfolk QOL-DN Norfolk Quality of Life–Diabetic Neuropathy, Q quartile, R-ODS Rasch-built Overall Disability Scale, SD standard deviation, SE standard error, TTR transthyretin, V30M Val30Met TTR variant

[a] The non-V30M TTR genotype represents 25 different variants in the HELIOS-A study

[b] Cardiac subpopulation was defined as patients who had pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)

[c] n = 37

[d] n = 26

Table 2 Treatment discontinuations across the NIS quartiles

	HELIOS-A Vutrisiran ($n = 122$)				APOLLO External placebo ($n = 77$)			
	Q1 ≥ 5.0 to ≤ 20.5 ($n = 38$)	Q2 > 20.5 to ≤ 44.1 ($n = 32$)	Q3 > 44.1 to ≤ 73.1 ($n = 30$)	Q4 > 73.1 to ≤ 127.0 ($n = 22$)	Q1 ≥ 5.0 to ≤ 20.5 ($n = 12$)	Q2 > 20.5 to ≤ 44.1 ($n = 18$)	Q3 > 44.1 to ≤ 73.1 ($n = 20$)	Q4 > 73.1 to ≤ 127.0 ($n = 27$)
Discontinuations, n (%)	0	2 (6.3)	4 (13.3)	0	3 (25.0)	7 (38.9)	6 (30.0)	13 (48.1)
Reason for discontinuation, n (%)								
Adverse event	0	0	0	0	1 (33.3)	2 (28.6)	1 (16.7)	3 (23.1)
Death	0	0	2 (50.0)	0	0	0	0	4 (30.8)
Other	0	2 (100.0)[a]	1 (25.0)[b]	0	0	0	0	0
Physician decision	0	0	1 (25.0)	0	0	0	0	2 (15.4)
Progressive disease	0	0	0	0	0	0	2 (33.3)	2 (15.4)
Withdrawal by patient	0	0	0	0	2 (66.7)	5 (71.4)	3 (50.0)	2 (15.4)

NIS Neuropathy Impairment Score, *Q* quartile

[a]Other reason for discontinuation reported as: patient withdrew informed consent ($n = 1$); patient withdrew from study due to disease progression and hospice ($n = 1$)

[b]Other reason for discontinuation reported as: withdrawal of consent from treatment. Health data collection still allowed ($n = 1$)

baseline NIS quartiles, patients in the external placebo group demonstrated clear worsening of polyneuropathy at Months 9 and 18 versus baseline, with the mean change in mNIS + 7 scores ranging between 12.1 and 33.1. Although vutrisiran-treated patients experienced benefit compared with external placebo in all baseline NIS quartiles, patients in the higher quartiles were unable to achieve similar mNIS + 7 scores compared with those in the lower quartiles at Months 9 and 18.

Norfolk QOL-DN Assessments by Baseline NIS Quartile

Baseline Norfolk QOL-DN scores were generally comparable between patients in the vutrisiran and external placebo groups within each baseline NIS quartile (Table 1). Vutrisiran demonstrated a beneficial treatment effect on Norfolk QOL-DN across all baseline NIS quartiles relative to the external placebo group, which was

first evident at Month 9 and continued through Month 18 (Fig. 2).

When change in neuropathy-related QOL from baseline was evaluated in different baseline NIS quartiles, vutrisiran-treated patients in Q1–Q3 showed improved QOL, as demonstrated by a negative mean change in Norfolk QOL-DN from baseline to 18 months (Fig. 2), and a relatively small deterioration of approximately 4.0 points was observed in patients in Q4 who had more severe neuropathy at baseline. In contrast, patients in the external placebo group experienced more prominent deterioration in their QOL for all baseline NIS quartiles; the mean change in Norfolk QOL-DN scores from baseline at Month 18 ranged between 10.9 and 25.6. Despite experiencing benefit relative to the external placebo group in all baseline NIS quartiles, vutrisiran-treated patients in the higher quartiles were unable to achieve the same level of QOL at 9 and 18 months compared with those in the lower quartiles.

		Q1: NIS ≥ 5.0 to ≤ 20.5			Q2: NIS > 20.5 to ≤ 44.1			Q3: NIS > 44.1 to ≤ 73.1			Q4: NIS > 73.1 to ≤ 127.0		
		BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
	n	38	38	37	32	32	29	30	24	25	22	22	21
Vutrisiran	Mean (± SE) Δ from baseline	—	−3.34 (2.10)	−2.95 (1.87)	—	−0.64 (2.44)	−3.07 (2.65)	—	−2.14 (3.00)	6.16 (3.13)	—	1.57 (2.31)	3.19 (2.81)
	n	12	11	9	18	13	11	20	19	15	27	24	16
Placebo	Mean (± SE) Δ from baseline	—	13.82 (6.39)	18.39 (7.87)	—	12.11 (2.95)	24.54 (4.04)	—	16.53 (3.88)	33.10 (6.16)	—	16.51 (3.87)	30.67 (6.15)
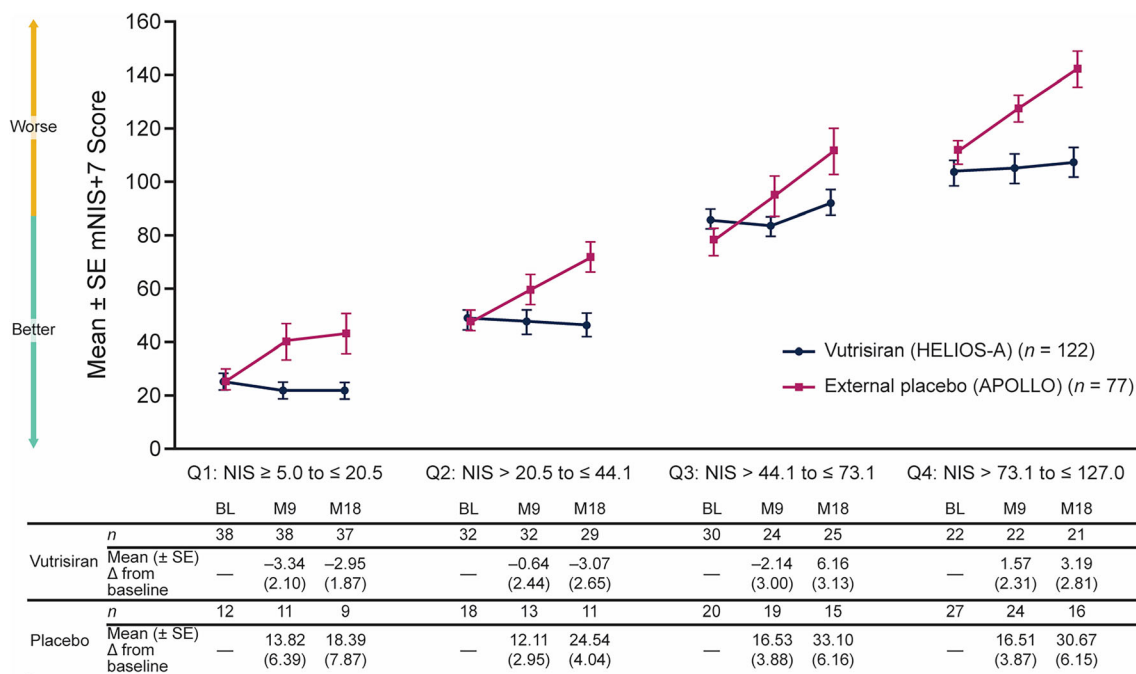
Fig. 1 Mean mNIS + 7 scores at baseline, 9 months, and 18 months according to baseline NIS quartile. *BL* baseline, *mNIS + 7* modified Neuropathy Impairment Score + 7, *M* Month, *NIS* Neuropathy Impairment Score, *Q* quartile, *SE* standard error

		Q1: NIS ≥ 5.0 to ≤ 20.5			Q2: NIS > 20.5 to ≤ 44.1			Q3: NIS > 44.1 to ≤ 73.1			Q4: NIS > 73.1 to ≤ 127.0		
		BL	M9	M18	BL	M9	M18	BL	M9	M18	BL	M9	M18
	n	37	37	36	32	32	29	30	24	25	22	22	21
Vutrisiran	Mean (± SE) Δ from baseline	—	−3.43 (2.72)	−2.00 (3.76)	—	−10.19 (2.89)	−6.41 (2.69)	—	−5.83 (4.38)	−3.60 (4.68)	—	4.64 (3.91)	3.95 (4.73)
	n	12	11	9	18	13	11	20	19	15	26	22	13
Placebo	Mean (± SE) Δ from baseline	—	4.18 (5.15)	10.89 (7.27)	—	13.69 (4.98)	25.64 (4.28)	—	16.05 (3.70)	18.00 (4.48)	—	9.91 (4.89)	24.54 (7.83)
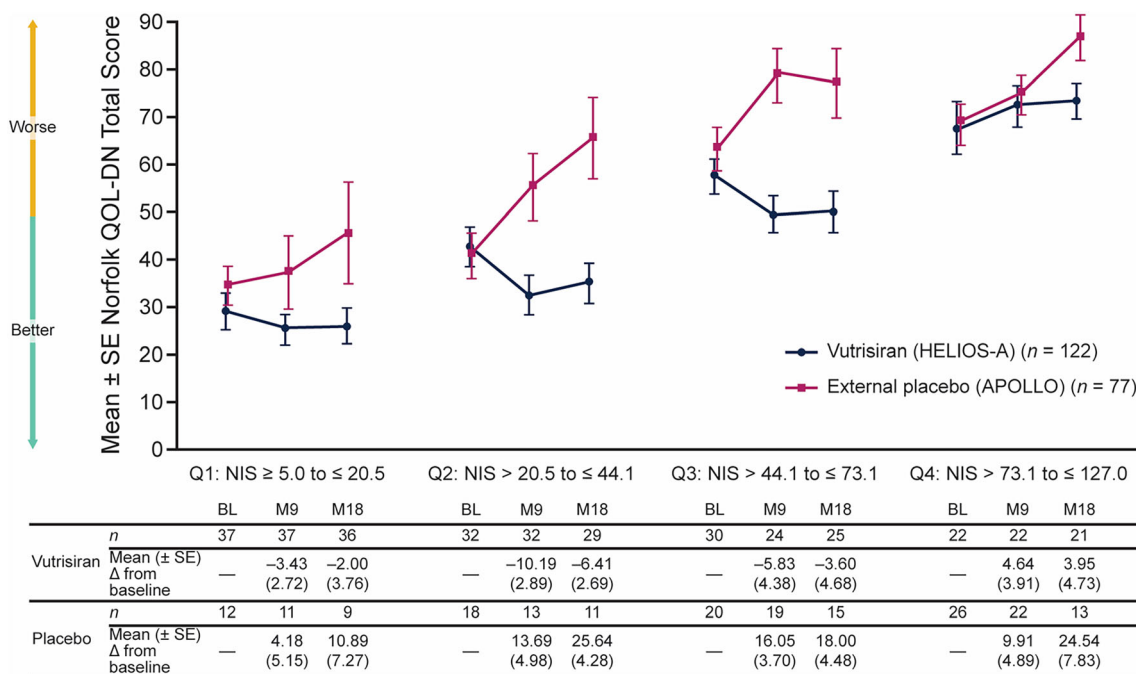
Fig. 2 Mean Norfolk QOL-DN total scores at baseline, 9 months, and 18 months according to baseline NIS quartile. *BL* baseline, *M* Month, *NIS* Neuropathy Impairment Score, *Norfolk QOL-DN* Norfolk Quality of Life–Diabetic Neuropathy, *Q* quartile, *SE* standard error
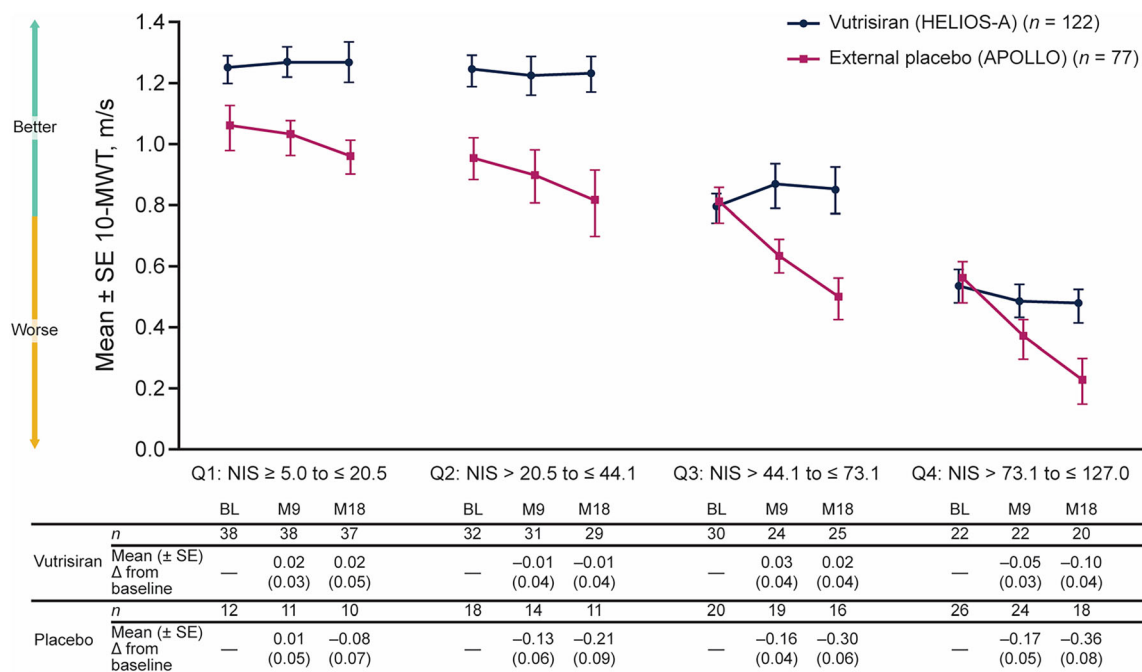
Fig. 3 Mean 10-MWT scores at baseline, 9 months, and 18 months according to baseline NIS quartile. *10-MWT* 10-m walk test, *BL* baseline, *M* Month, *NIS* Neuropathy Impairment Score, *Q* quartile, *SE* standard error

Functional Measures (Gait Speed, R-ODS) and Nutritional Status (mBMI) Assessments by Baseline NIS Quartile

Baseline gait speed values in the vutrisiran and external placebo groups were comparable for Q3 and Q4, whereas, in the vutrisiran group, higher values were observed in Q1 and Q2 compared with the external placebo group (Table 1). In vutrisiran-treated patients, 10-MWT results remained stable in Q1–Q3 versus baseline, and patients in Q4 demonstrated a modest decline over 18 months (Fig. 3), whereas, in the external placebo group, there was a substantial decline in gait speed, which increased with each increasing quartile. Overall, vutrisiran treatment demonstrated a beneficial effect compared with external placebo across all baseline NIS quartiles, which was evident by 9 months for Q2–Q4.

Baseline R-ODS scores were generally comparable between the vutrisiran and the external placebo groups within each baseline NIS quartile (Table 1). For vutrisiran-treated patients, R-ODS scores remained relatively stable over 18 months across all baseline NIS quartiles, with a modest worsening in Q3 and Q4 versus baseline (Fig. 4). However, in the external placebo group, R-ODS showed clear worsening versus baseline over 18 months across all quartiles, with a larger decline observed with each increasing quartile. Vutrisiran showed a beneficial effect on R-ODS across all baseline NIS quartiles, relative to the external placebo group, which was first evident at Month 9.

For mBMI, baseline scores were comparable for the vutrisiran and the external placebo group within each baseline NIS quartile (Table 1). mBMI remained relatively stable over 18 months in vutrisiran-treated patients across all baseline NIS quartiles, with modest improvements from baseline in patients in Q1–Q3 and a small deterioration in patients in Q4 at 18 months (Fig. 5). Patients in the external placebo group experienced a relatively larger decline from baseline in mBMI across all baseline NIS quartiles. Thus, vutrisiran-treated patients experienced a treatment benefit on mBMI over the external placebo group across all baseline NIS quartiles over 18 months, which was first evident at Month 9.
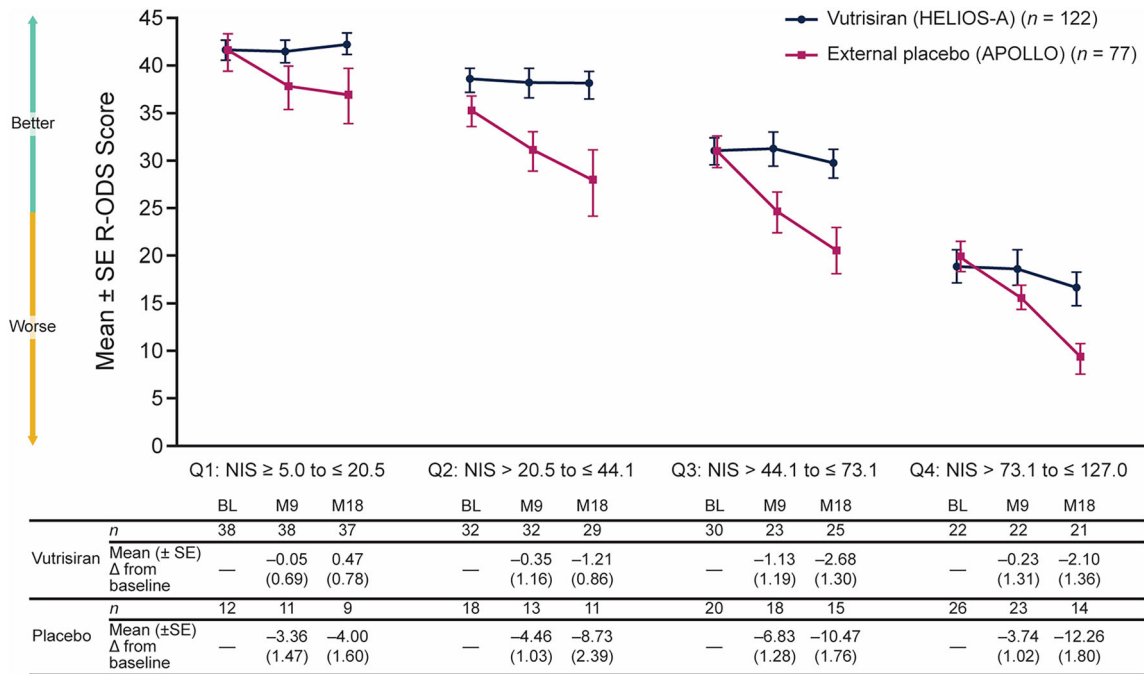
Fig. 4 Mean R-ODS scores at baseline, 9 months, and 18 months according to baseline NIS quartile. *BL* baseline, *M* Month, *NIS* Neuropathy Impairment Score, *Q* quartile, *R-ODS* Rasch-built Overall Disability Scale, *SE* standard error
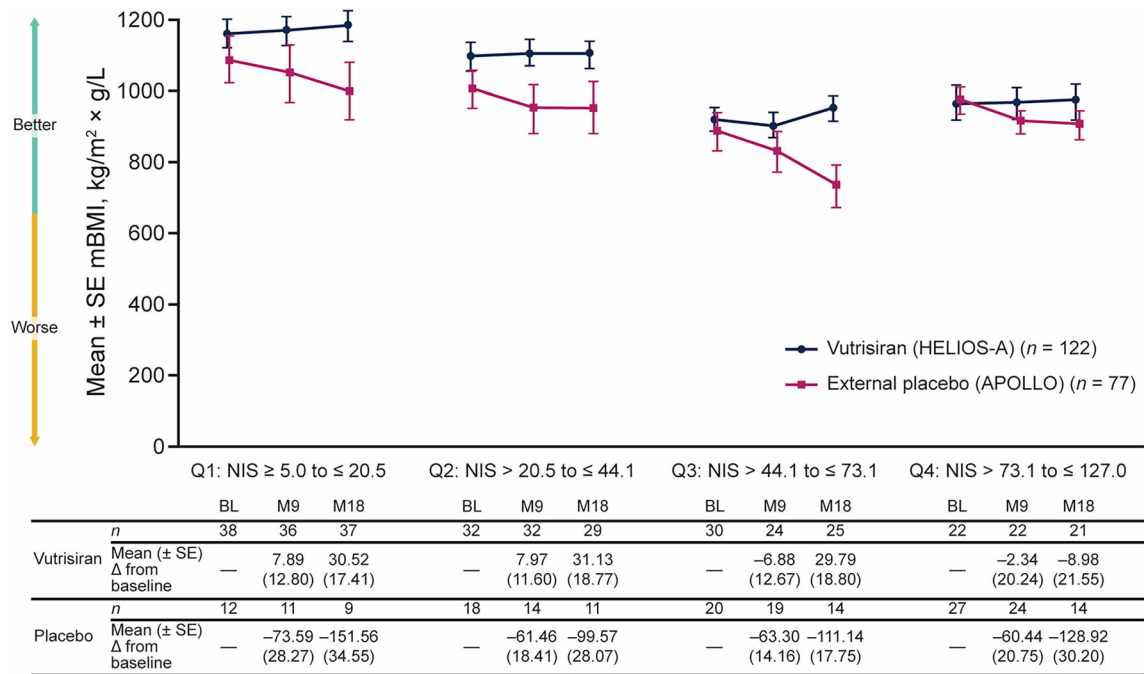
Fig. 5 Mean mBMI at baseline, 9 months, and 18 months according to baseline NIS quartile. *BL* baseline, *mBMI* modified body mass index, *M* Month, *NIS* Neuropathy Impairment Score, *Q* quartile, *SE* standard error

DISCUSSION

This post hoc analysis assessed the impact of baseline neuropathy severity on the outcomes of neurologic function, QOL, disability, and nutritional status in vutrisiran-treated patients with ATTRv amyloidosis with polyneuropathy from the HELIOS-A study compared with an external placebo group from the APOLLO study. Overall, vutrisiran demonstrated a beneficial treatment effect compared with external placebo for all endpoints at Month 18 across all subgroups of baseline neuropathy severity.

In the vutrisiran group, there was a trend for improvement or stabilization at Month 18 versus baseline across the different disease outcomes in patients from most baseline NIS quartiles. Although a modest amount of worsening was observed for some of the outcomes in patients who had more severe neuropathy at baseline (Q3 and/or Q4), vutrisiran continued to demonstrate a beneficial effect compared with external placebo even in those quartiles. In general, patients who had more severe neuropathy at baseline (Q3 and Q4) were not able to recover to the same level of function as those who initiated vutrisiran treatment earlier in their disease course (Q1 and Q2). These results demonstrate that earlier intervention allows greater opportunity to improve or stabilize disease-related endpoints, highlighting the benefits of early diagnosis and treating patients early in their disease course.

These observations also mirror those demonstrated in a similar post hoc analysis from the APOLLO study, where treatment benefit with another RNAi therapeutic, patisiran, versus placebo was demonstrated in patients with ATTRv amyloidosis across the full range of baseline NIS quartiles [25]. Previous studies evaluating the effect of TTR stabilizers on the NIS-Lower Limb or NIS assessments similarly found that patients with lower baseline disease severity were likely to have the greatest response to treatment, and thus the slowest disease progression [31–33]. Further, during the Italian compassionate use program for inotersen, patients with familial amyloid polyneuropathy (FAP) stage 1 at baseline demonstrated disease stability over 24 months, whereas those with FAP stage 2 at baseline showed worsening disease stage following treatment with inotersen [34]. Taken together, these data re-iterate the need for early and accurate diagnosis, and rapid treatment initiation in order to delay disease progression.

The availability of disease-modifying treatments, such as *TTR* gene silencers, has changed the treatment landscape of ATTRv amyloidosis [35]. In addition to these advanced treatment options, disease awareness has improved, leading to earlier diagnosis of patients [36–38], which—along with treating early to delay clinical progression and preserve QOL—is one of the key goals of disease management [35]. Our results are in line with these treatment goals and reinforce the benefits of vutrisiran, a disease-modifying treatment, across a wide range of baseline neuropathy severities.

Certain limitations when interpreting the data should be noted, including the post hoc nature of the analysis and its lack of power to report significant differences between the groups within each baseline NIS quartile due to the small sample sizes. Another limitation was the use of an external placebo control rather than a within-trial placebo group, although the APOLLO and HELIOS-A studies had similar eligibility criteria. Finally, the rate of study discontinuation in the HELIOS-A vutrisiran arm was low (4.1%) and similar to other studies conducted in the same patient population, and it was not considered to have an impact on the interpretation of the results of the current analysis.

CONCLUSIONS

Vutrisiran provides treatment benefits compared with external placebo across a range of disease-relevant outcomes regardless of baseline neuropathy severity. Furthermore, our data demonstrate the importance of early diagnosis and treatment to give patients the best opportunity to achieve stabilized or improved function and/or QOL in the progressive and debilitating disease process of ATTRv amyloidosis.

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