

## Patisiran: Hospitalization and Mortality

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### SUMMARY

- APOLLO-B was a phase 3 study designed to evaluate the efficacy and safety of patisiran (n=181) versus placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR.<sup>1</sup>
  - The secondary composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits) and change from baseline in 6-MWT over 12 months resulted in a win ratio of 1.27 (95% CI: 0.99, 1.61) and was not significant.<sup>1</sup>
  - In the 12-month treatment period, deaths were observed in 4 (2.2%) and 10 (5.6%) patients in the patisiran and placebo arms, respectively, with an estimated HR of 0.36 (95% CI: 0.11, 1.14).<sup>1</sup>
- APOLLO was a phase 3 study designed to assess the efficacy and safety of patisiran (n=148) versus placebo (n=77) in patients with hATTR-PN. A post-hoc analysis of the APOLLO safety data was conducted in the mITT population.<sup>2,3</sup>
  - The exposure-adjusted rates of all-cause hospitalization and/or all-cause mortality were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran arms, respectively.<sup>3</sup>
  - The exposure-adjusted rates of cardiac hospitalizations and/or all-cause mortality were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran arms, respectively.<sup>3</sup>
- The Global OLE study (N=211) was a study designed to evaluate the long-term safety and efficacy of patisiran in patients with hATTR-PN. Patients with hATTR-PN who completed the patisiran Phase 2 OLE study or phase 3 APOLLO study and met eligibility criteria were able to start or continue patisiran for up to 5 years.<sup>4</sup>
  - The exposure-adjusted mortality rate per 100 patient-years was 12.8 (95% CI, 8.2-19.8) in the APOLLO-placebo group, 3.3 (95% CI, 2.3-4.9) in the APOLLO-patisiran group, and 1.7 (95% CI, 0.5-5.2) in the Phase 2 OLE-patisiran group.<sup>4</sup>
  - Post-hoc analyses in a pooled cardiac population of patients across the Global OLE and APOLLO-B OLE were conducted to evaluate the long-term effect of patisiran on survival and all-cause hospitalizations.<sup>5</sup>

**APOLLO-B**

APOLLO-B was a multicenter, randomized (1:1), double-blind, placebo-controlled, phase 3 study designed to evaluate the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=181) versus placebo (n=179) in patients with ATTR-CM, including both hATTR and wtATTR. The primary endpoint was the change from baseline in the 6-MWT at 12 months. After the 12-month double-blind treatment period, all eligible patients received patisiran in an open-label extension period.<sup>1</sup>

**Patient Demographics and Baseline Characteristics**

The baseline demographic and clinical characteristics were generally balanced between the patisiran and placebo arms and representative of the global population of patients with ATTR-CM. Across both groups of patients, the median age was 76 years, majority were men, and 25% received tafamidis at baseline. Approximately 80% of patients in each group had wtATTR. Among the patients with hATTR, there were 16 different pathogenic TTR variants. Most patients were NYHA class II (patisiran 86%, placebo 84%) and ATTR amyloidosis Stage 1 (patisiran 69%, placebo 67%).<sup>1</sup>

**Secondary Composite Endpoints over 12 Months**

The secondary composite endpoint of all-cause mortality, frequency of CV events (CV hospitalizations and urgent HF visits) and change from baseline in 6-MWT over 12 months resulted in a win ratio of 1.27 (95% CI: 0.99, 1.61) and did not significantly differ between patisiran and placebo.<sup>1</sup> **Table 1** includes a summary of the secondary composite endpoints over 12 months.<sup>6</sup>

**Table 1. Secondary Composite Outcome Endpoints over 12 Months.<sup>6</sup>**

	Patisiran	Placebo
<b>Composite of death from any cause, frequency of CV events,<sup>a</sup> and change from baseline in 6-MWT over 12 months<sup>b</sup></b>		
Stratified win ratio (95% CI) for patisiran vs. placebo <sup>c</sup>	1.27 (0.99, 1.61)	
<b>Composite of death from any cause and frequency of hospitalizations for any cause and urgent visits for HF in patients not on tafamidis at baseline<sup>b</sup></b>		
Number of patients	135	133
Total number of events, n	57	55
Death from any cause	3	7
Hospitalizations for any cause	50	47
Urgent visits for HF	4	1
HR (95% CI) for patisiran vs. placebo <sup>d,e</sup>	0.997 (0.62, 1.60)	
Incidence rate ratio (patisiran/placebo) <sup>d,f</sup>	0.97 (0.58, 1.63)	
<b>Composite of death from any cause and frequency of hospitalizations for any cause and urgent visits for HF in the overall population<sup>b</sup></b>		
Number of patients	181	178
Total number of events, n	73	79
Death from any cause	4	10
Hospitalizations for any cause	65	65
Urgent visits for HF	4	4
HR (95% CI) for patisiran vs. placebo <sup>d,e</sup>	0.88 (0.58, 1.34)	
Incidence rate ratio (patisiran/placebo) <sup>d,f</sup>	0.87 (0.55, 1.36)	

Abbreviations: 6-MWT = 6-minute walk test; ATTR = transthyretin amyloidosis; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NYHA = New York Heart Association.

<sup>a</sup>CV events were defined as CV hospitalizations and urgent visits for HF.

<sup>b</sup>Deaths, hospitalizations, and urgent visits for HF due to COVID-19 were not treated as events in the analysis, in accordance with the pre-defined statistical analysis plan. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in the analysis.

<sup>c</sup>The first composite end point was analyzed using a generalized rank-based win ratio method stratified by baseline tafamidis use (yes vs. no), which made within-stratum pairwise comparisons for all possible patisiran–placebo patient pairs in a sequential manner (first mortality, then CV events, then 6-MWT).

<sup>d</sup>Patients who died due to COVID-19 (1 patisiran patient) were censored at the date of death, and cardiac transplants were handled in the same manner as death (two placebo patients).

<sup>e</sup>The HR and 95% CI were derived using an Andersen–Gill model, including treatment arm, type of ATTR, baseline NYHA class, and age group as covariates. For the analysis in the overall population, the model was also stratified by baseline tafamidis use. A HR less than 1 represents a favorable outcome for patisiran.

<sup>f</sup>The incidence rate ratio and 95% CI were derived using a negative binomial model, including treatment arm, type of ATTR, baseline NYHA class, and age group as covariates. For the analysis in the overall population, the model also included baseline tafamidis use and the treatment-by-baseline tafamidis use interaction as covariates. An incidence rate ratio less than 1 represents a favorable outcome for patisiran. CI widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

### Mortality Over 12 Months

In the overall population of the APOLLO-B study, 4 deaths (2.2%) occurred in the patisiran group and 10 deaths (5.6%) occurred in the placebo group. The estimated HR (patisiran-to-placebo) was 0.36 (95% CI, 0.11 to 1.14). Two patients (1.1%) from the placebo group received heart transplants, which were counted as deaths in the efficacy analysis. Data for a patient who died from COVID-19 (1 patient [0.56%] in the patisiran group) were censored at the date of death, and this death was not included as an event in the efficacy analysis.<sup>1</sup>

## APOLLO

APOLLO was a multicenter, international, randomized (2:1), double-blind, placebo-controlled, phase 3 study designed to assess the efficacy and safety of IV patisiran 0.3 mg/kg every 3 weeks (n=148) versus placebo (n=77) in patients with hATTR-PN. The primary endpoint was the change from baseline in the mNIS+7 at 18 months.<sup>2</sup>

### Patient Demographics and Baseline Characteristics

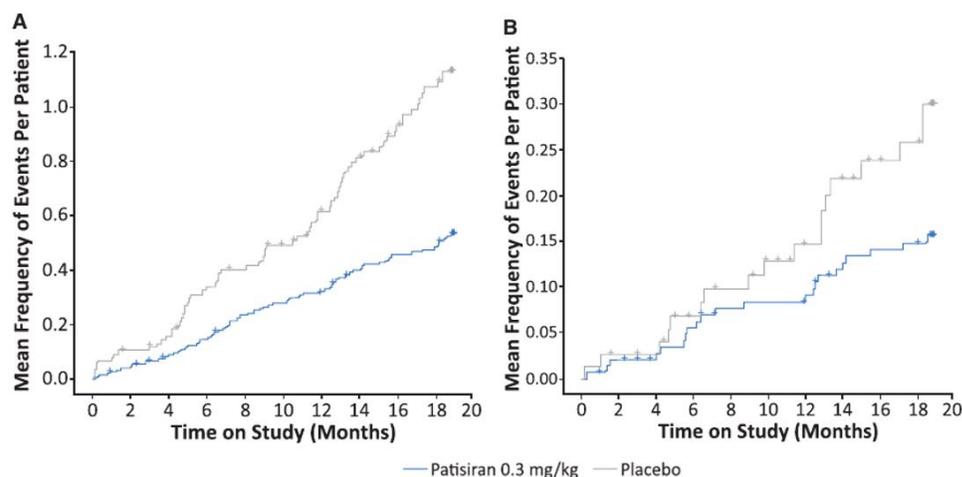
The baseline demographics and clinical characteristics were generally well-balanced between the patisiran and placebo arms. Across both groups, the median age was 62 years, 74% of patients were male, and 72% were white/Caucasian. The median time to diagnosis in the patisiran group was 1.3 years and 1.4 years in the placebo group. Most patients in both groups were in FAP stage 1 (patisiran, 45%, placebo 48%) or FAP stage 2 (patisiran 55%, placebo 51%). There was a similar distribution between groups by NYHA class: NYHA class I (patisiran 47%, placebo 52%) and NYHA class II (patisiran 52%, placebo 47%).<sup>2</sup>

### Post-Hoc Analyses of Hospitalization and Mortality

Post-hoc analyses of the APOLLO study were conducted in the mITT population (N=225) to assess the composite of all-cause hospitalization and/or all-cause mortality and the composite of cardiac hospitalization and/or all-cause mortality. The mITT population was defined as all randomized patients who received  $\geq 1$  dose of study drug. All-cause hospitalization and mortality were defined as any hospitalization or death associated with a SAE that occurred within 28 days of the last dose of study drug (placebo or patisiran). Cardiac hospitalizations were defined as any SAE coded to cardiac disorders that led to hospitalization or prolongation of an existing hospitalization. For these events of interest, the exposure-adjusted event rates were estimated for patients treated with either placebo or patisiran.<sup>3</sup>

The exposure-adjusted rates of the composite of all-cause hospitalization and/or death were 71.8 and 34.7 per 100 patient-years in the placebo and patisiran groups, respectively. The rates of the composite of cardiac hospitalizations and all-cause death were 18.7 and 10.1 per 100 patient-years in the placebo and patisiran groups, respectively. Patisiran was associated with an approximate reduction of 50% for all-cause hospitalization and mortality and an approximate reduction of 45% for cardiac hospitalization and all-cause mortality (**Figure 1**).<sup>3</sup>

**Figure 1. Composite Rates of Hospitalization and Mortality Events Per Patient from Baseline to Month 18.<sup>3</sup>**



Abbreviations: CI = confidence interval; HR = hazard ratio; RR = rate ratio.

A) Composite rate of all-cause hospitalization and mortality. Negative binomial regression RR, 0.49 (95% CI, 0.30–0.79); Andersen–Gill HR, 0.48 (95% CI, 0.34–0.69).

B) Composite rate of cardiac hospitalization and all-cause mortality. Negative binomial regression RR, 0.54 (95% CI, 0.25–1.16); Andersen–Gill HR, 0.54 (95% CI, 0.28–1.01).

From Solomon et al.<sup>3</sup>

## GLOBAL OLE

The Global OLE study was a multicenter, international study designed to evaluate the long-term safety and efficacy of IV patisiran in patients with hATTR-PN. Patients with hATTR-PN who completed the patisiran Phase 2 OLE study or phase 3 APOLLO study and met eligibility criteria were able to start or continue IV patisiran 0.3 mg/kg every 3 weeks for up to 5 years. The study enrolled 25 patients from the patisiran Phase 2 OLE study (Phase 2 OLE-patisiran group), 137 patients from the APOLLO-patisiran arm (APOLLO-patisiran group), and 49 patients from the APOLLO-placebo arm (APOLLO-placebo group).<sup>4</sup>

### Patient Demographics and Baseline Characteristics

At Global OLE enrollment, patients in the APOLLO-placebo group had higher levels of NT-proBNP and more severe polyneuropathy than patients in the APOLLO-patisiran and Phase 2 OLE-patisiran groups. Across the study populations, the mean age was 61.3 years, and 73.9% of patients were male. There was a higher proportion of patients in the Phase 2 OLE-patisiran group with the V30M genotype compared with the APOLLO-placebo and APOLLO-patisiran groups. Additional baseline disease characteristics are presented in **Table 2**.<sup>4,7</sup>

**Table 2. Select Baseline Characteristics at Global OLE Enrollment.<sup>7</sup>**

Characteristic	APOLLO- placebo (n=49)	APOLLO- patisiran (n=137)	Phase 2 OLE- patisiran (n=25)	Global OLE Total (n=211)
Genotype, n (%)				
Early-onset V30M	7 (14.3)	13 (9.5)	10 (40.0)	30 (14.2)
Late-onset V30M	17 (34.7)	43 (31.4)	8 (32.0)	68 (32.2)
Non-V30M	25 (51.0)	81 (59.1)	7 (28.0)	113 (53.6)
NIS, mean (SD)	81.5 (41.7)	62.3 (37.9)	35.5 (28.7)	63.6 (39.9)
Norfolk QOL-DN, mean (SD)	72.7 (28.1)	54.5 (30.9)	34.0 (NC) <sup>a</sup>	59.2 (31.1)
FAP stage, n (%)				
I	14 (28.6)	58 (42.3)	20 (80.0)	92 (43.6)
II	27 (55.1)	71 (51.8)	5 (20.0)	103 (48.8)
III	8 (16.3)	8 (5.8)	0	16 (7.6)
IV	0	0	0	0
PND score, n (%)				
0	0	1 (0.7)	0	1 (0.5)
I	7 (14.3)	32 (23.4)	10 (40.0)	49 (23.2)
II	9 (18.4)	36 (26.3)	13 (52.0)	58 (27.5)
IIIA	8 (16.3)	33 (24.1)	1 (4.0)	42 (19.9)
IIIB	17 (34.7)	27 (19.7)	1 (4.0)	45 (21.3)
IV	8 (16.3)	8 (5.8)	0	16 (7.6)
NYHA classification, n (%)				
I	22 (44.9)	67 (48.9)	19 (76.0)	108 (51.2)
II	21 (42.9)	59 (43.1)	4 (16.0)	84 (39.8)
III	4 (8.2)	9 (6.6)	2 (8.0)	15 (7.1)
IV	2 (4.1)	2 (1.5)	0	4 (1.9)
NAC ATTR amyloidosis stage, n (%)				
1	39 (79.6)	118 (86.1)	25 (100)	182 (86.3)
2	9 (18.4)	17 (12.4)	0	26 (12.3)
3	1 (2.0)	2 (1.5)	0	3 (1.4)
NT-proBNP, mean (SD), ng/mL	1957.6 (2731.3)	1017.2 (1558.8)	281.9 (422.0)	1148.5 (1884.8)

Abbreviations: FAP = familial amyloid polyneuropathy; NAC = National Amyloidosis Centre; NC = not calculable; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PND = polyneuropathy disability; SD = standard deviation.

<sup>a</sup>n=1; Norfolk QOL-DN was not collected in the Phase 2 OLE.

## Mortality

### 5-Year Results

Post-hoc analyses of survival were conducted based on AE data and assessed using Kaplan-Meier analysis. Exposure-adjusted mortality rates were calculated as the total number of deaths per 100 patient-years and only included deaths following the first dose of patisiran.<sup>4</sup>

During the Global OLE, death was reported in 41 (19.4%) patients. None of the deaths were considered related to patisiran by the investigators. Survival rates were higher among patients who received patisiran in their parent studies compared with those who received placebo in the parent study and switched to patisiran upon entering the Global OLE. The exposure-adjusted mortality rate per 100 patient-years was 12.8 (95% CI, 8.2-19.8) in the APOLLO-placebo group, 3.3 (95% CI, 2.3-4.9) in the APOLLO-patisiran group, 1.7 (95% CI, 0.5-5.2) in the Phase 2 OLE-patisiran group, and 4.4 (95% CI, 3.3-5.8) in the overall Global OLE population.<sup>4</sup>

Risk factors for mortality at parent study baseline were evaluated and univariate analyses identified associations between mortality and select baseline characteristics. Post-hoc multivariate Cox proportional hazards analyses were conducted using factors that were significant in the univariate model. In both full and selection-based multivariate analyses, FAP stage and parent study treatment were associated with mortality (**Table 3**).<sup>4</sup>

**Table 3. Multivariate Analyses of Risk Factors for Mortality in the Global OLE.**<sup>4</sup>

Characteristics at parent study baseline	Selection-based analysis (n=220) <sup>a</sup>		Full analysis (n=220) <sup>b</sup>	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Parent study treatment (placebo vs. patisiran)	5.19 (2.79-9.63)	<0.001	5.52 (2.91-10.48)	<0.001
FAP stage II/III vs. I	5.74 (2.76-11.92)	<0.001	4.89 (1.69-14.12)	0.003
Genotype				
Late-onset V30M vs. early-onset V30M	0.83 (0.16-4.42)	0.83	0.88 (0.16-4.75)	0.88
Non-V30M vs. early-onset V30M	2.22 (0.44-11.19)	0.34	2.36 (0.47-12.00)	0.30
NT-proBNP, >3000 ng/L vs. ≤3000 ng/L	3.57 (0.95-13.38)	0.06	3.16 (0.75-13.29)	0.12
Mean LV wall thickness ≥1.5 cm vs. <1.5 cm	1.96 (0.82-4.71)	0.13	1.60 (0.50-5.11)	0.43
NAC ATTR stage 2/3 vs. 1	2.97 (0.86-10.20)	0.08	3.54 (0.91-13.69)	0.07
LV mass ≥243.67 g vs. <243.67 g	NA	NA	1.12 (0.46-2.73)	0.80
NYHA classification II vs. I	NA	NA	1.19 (0.61-2.30)	0.61
Cardiac subpopulation, yes vs. no	NA	NA	1.41 (0.72-2.76)	0.31
NIS score ≥56.58 vs <56.68	NA	NA	1.80 (0.84-3.65)	0.13
PND score III/IV vs. I/II <sup>c</sup>	NA	NA	0.81 (0.36-1.84)	0.62

Abbreviations: ATTR = transthyretin amyloidosis; CI = confidence interval; FAP = familial amyloid polyneuropathy; HR = hazard ratio; LV = left ventricular; NA = not applicable; NAC = National Amyloidosis Centre; NIS = Neuropathy Impairment Score; NT-proBNP = N-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability.

<sup>a</sup>The P-value threshold for entry to or removal from the selection-based multivariate Cox proportional hazards analysis was set at 0.15. Forward, backward, and stepwise selection-based models all led to the same variables being selected.

<sup>b</sup>Full multivariate Cox proportional hazards analysis was conducted using factors that were significant (P<0.05) in a univariate model. Survival time is calculated as time from parent study baseline to death or last known alive date on or before end of study.

<sup>c</sup>PND scores are defined as follows: I, preserved walking and sensory disturbances; II, impaired walking without the need for a stick or crutches; IIIA, walking with 1 stick or crutch; IIIB, walking with 2 sticks or crutches; and IV, confined to a wheelchair or bedridden.

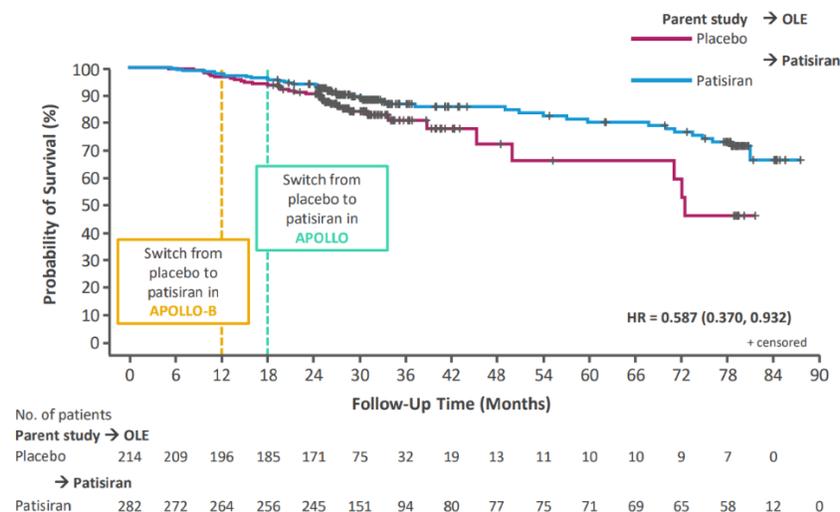
## POOLED ANALYSES

Post-hoc analyses of a pooled cardiac population of patients across patisiran clinical studies were conducted to evaluate the long-term effect of patisiran on survival, hospitalizations, and cardiac parameters. The pooled cardiac population consisted of patients with hATTR-PN from the Global OLE that had a baseline LV wall thickness ≥13 mm and an absence of history of aortic valve disease or hypertension, in addition to all patients with ATTR-CM from the APOLLO-B OLE.<sup>5</sup>

### Survival and Hospitalization

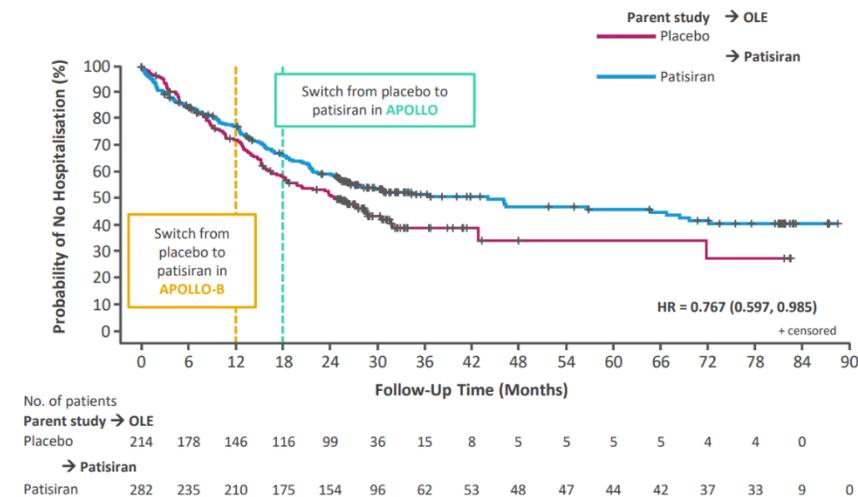
The probabilities of survival and all-cause hospitalizations by initial treatment arm are shown in **Figures 2 and 3**, respectively.<sup>5</sup>

**Figure 2. Survival by Initial Treatment Arm in the Pooled Cardiac Populations.**<sup>5</sup>



Abbreviations: HR = hazard ratio; OLE = open-label extension.  
From Lairez et al.<sup>5</sup>

**Figure 3. Hospitalizations by Initial Treatment Arm in the Pooled Cardiac Populations.**<sup>5</sup>



Abbreviations: HR = hazard ratio; OLE = open-label extension.  
From Lairez et al.<sup>5</sup>

## ABBREVIATIONS

6-MWT = 6-minute walk test; AE = adverse event; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CI = confidence interval; CV = cardiovascular; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; HF = heart failure; HR = hazard ratio; IV = intravenous; LV = left ventricular; mITT = modified intent-to-treat; mNIS+7 = modified Neuropathy Impairment Score +7; NAC = National Amyloidosis Centre; NC = not calculable; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; OLE = open-label extension; PND = polyneuropathy disability; RR = rate ratio; SAE = serious adverse event; SD = standard deviation; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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