Vutrisiran: Randomized Treatment Extension Period of the HELIOS-A Study

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SUMMARY

- HELIOS-A was a phase 3, global, randomized, open-label study designed to assess the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months.[1]
- After the 18-month treatment period of the HELIOS-A study, all eligible patients entered an open-label RTE period and were randomized 1:1 to either vutrisiran 25 mg every 3 months or vutrisiran 50 mg every 6 months for up to an additional 42 months.[2]
    - A protocol amendment was initiated to transition all patients on vutrisiran 50 mg every 6 months to vutrisiran 25 mg every 3 months.[2]
- From RTE baseline to Month 18, treatment with vutrisiran demonstrated sustained clinical efficacy in endpoints including mNIS+7, Norfolk QOL-DN, 10-MWT, mBMI, R-ODS, and PND score.[2]
- At Month 42 of the RTE period, a consistent effect was observed in serum TTR reduction in patients who transitioned from patisiran (patisiran/vutrisiran) and in patients who had received vutrisiran for the entire study (vutrisiran/vutrisiran).[2]
- During the RTE period, the majority of AEs reported with vutrisiran were mild or moderate in severity.[2]

INDEX

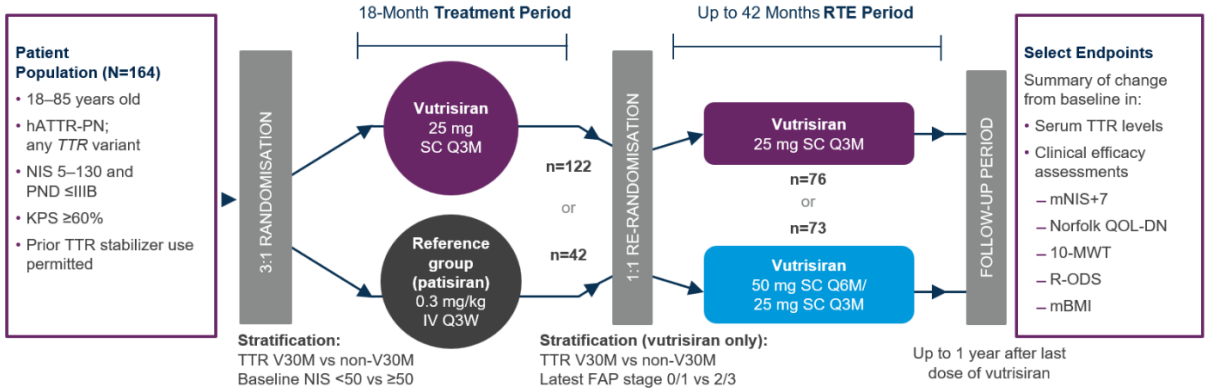
STUDY DESIGN

HELIOS-A was a phase 3, global, randomized, open-label study designed to assess the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. After the 18-month treatment period was completed, all eligible patients, including those on patisiran, entered the RTE and were randomized 1:1

to receive either vutrisiran 25 mg every months or vutrisiran 50 mg every 6 months by subcutaneous injection (**Figure 1**).[1,3]

During the RTE period, a protocol amendment was enacted to transition patients on vutrisiran 50 mg every 6 months to vutrisiran 25 mg every 3 months due to serum TTR recovery observed at the end of the 50 mg every 6 months dosing interval compared with the 25 mg every 3 months dosing interval. The first patient transitioned on Day 505 of the RTE.[2]

Figure 1. HELIOS-A RTE Study Design.[3]



Abbreviations: 10-MWT = 10-meter walk test; FAP = familial amyloid polyneuropathy; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; KPS = Karnofsky Performance Status; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; NIS = Neuropathy Impairment Score; Norfolk QOL-DN = Norfolk Quality of Life-Diabetic Neuropathy; PND = polyneuropathy disability; Q3M = every 3 months; Q3W = every 3 weeks; Q6M = every 6 months; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension; SC = subcutaneous; TTR = transthyretin.
From Cauquil et al.[3]

At the final database lock (December 24, 2025), 130 patients (87.2%) had completed treatment, and 19 patients (12.8%) had discontinued treatment. A total of 21 patients (14.1%) discontinued the study, with death (n=12, 8.1%) being the most common reason.[2]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

The baseline demographics and disease characteristics of patients at HELIOS-A RTE enrollment are summarized in **Table 1**.[2]

Table 1. HELIOS-A RTE Baseline Demographics and Disease Characteristics.[2]

Characteristic	Total Vutrisiran (n=149)
Age, years, median (range)	62.0 (33.0-83.0)
Male, n (%)	93 (62.4)
Race, n (%)	
White	105 (70.5)
Asian	27 (18.1)
Other[a]	17 (11.4)
Age at hATTR symptom onset <50 years, n (%)	54 (36.2)
TTR genotype	
V30M, n (%)	69 (46.3)
non-V30M[b], n (%)	80 (53.7)
Early-onset V30M (<50 years), n (%)	30 (20.1)
Previous TTR stabilizer use, n (%)	98 (65.8)

Characteristic	Total Vutrisiran (n=149)
NIS <50, n (%)	94 (63.1)
FAP stage ≥II, n (%)	42 (28.2)
PND score ≥III, n (%)	39 (26.2)
NYHA class III or IV, n (%)	13 (8.7)
NT-proBNP >3000 ng/L, n (%)	10 (6.7)
Serum TTR, mg/L, mean (SE)	209.61 (4.99)

Abbreviations: FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; mBMI = modified body mass index; NIS = Neuropathy Impairment Score; NT-proBNP = *N*-terminal prohormone of brain-type natriuretic peptide; NYHA = New York Heart Association; PND = polyneuropathy disability; Q3M = every 3 months; Q6M = every 6 months; RTE = randomized treatment extension; TTR = transthyretin.

[a]Includes Black/African American, ≥2 races, and other races.

[b]Non-V30M variants included T60A (n=17); E89Q (n=12); A97S (n=8); D38A, S50R and V122I (all n=5); L58H and S77Y (both n=4); I107V (n=3); S52P and S77F (both n=2); and A45V, R34T, D39V, E42G, E61K, G47A, K35N, K55N, F64L, T106N, T59K, Y114C and V28M (all n=1).

PHARMACODYNAMIC RESULTS

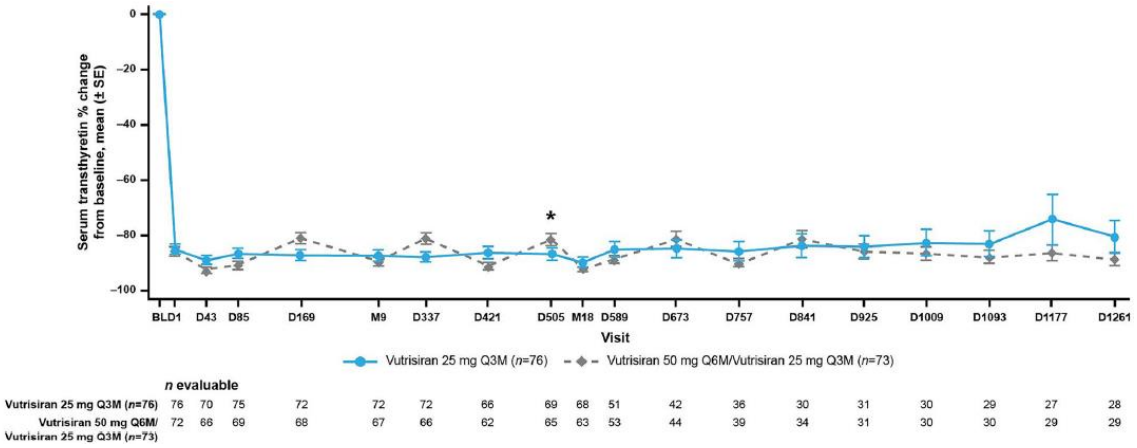
Vutrisiran 25 mg Q3M vs. Vutrisiran 50 mg Q6M

Serum TTR Level

At Month 9 of the RTE, the 95% CI for the median treatment difference in percentage of serum TTR reduction was estimated with the Hodges-Lehmann method, stratified by previous stabilizer use (yes vs no). Non-inferiority of vutrisiran 50 mg every 6 months versus vutrisiran 25 mg every 3 months was established as the H-L median difference (95% CI) between the two arms was 0.58 (-1.28, 2.92), in which the lower 95% CI limit was above the prespecified non-inferiority margin of -10%.[2]

Recovery of serum TTR was noted at the end of the vutrisiran 50 mg every 6 months dosing interval when compared with the 25mg every 3 months dose; thus, a protocol amendment was initiated to transition all patients on vutrisiran 50 mg every 6 months to vutrisiran 25 mg every 3 months. The decision to transition was unrelated to safety concerns. The mean percent change in serum TTR from baseline during the RTE period is shown in **Figure 2**.[2]

Figure 2. Mean (±SE) Percent Change from Baseline in Serum TTR During the RTE.[2]



Abbreviations: BL = baseline; D = day; M = month; Q3M = every 3 months; Q6M = every 6 months; RTE = randomized treatment extension; SE = standard error; TTR = transthyretin.

*Time point at which the first patient transitioned from vutrisiran 50 mg Q6M to vutrisiran 25 mg Q3M.

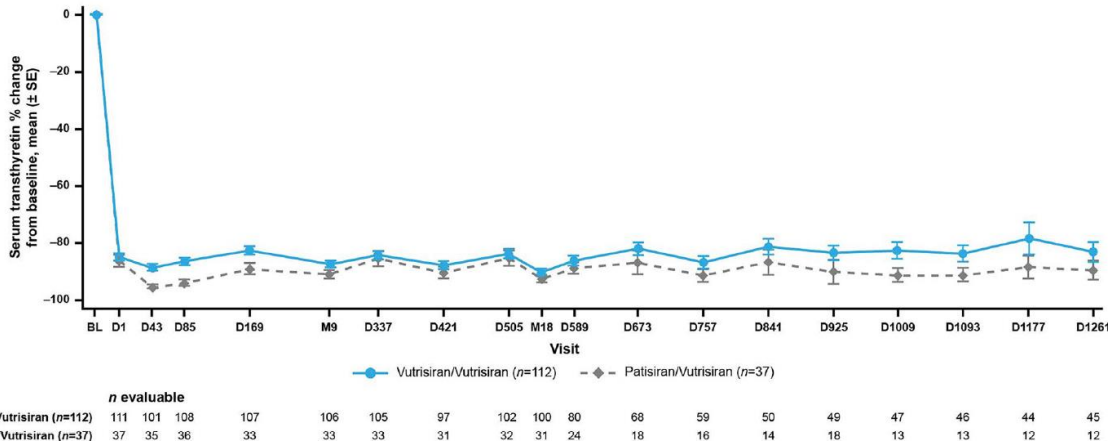
From Cauquil et al.[2]

Switch from Patisiran to Vutrisiran

Serum TTR Level

A sustained TTR reduction was observed in patients who received patisiran during the 18-month treatment period and in the patients who transitioned to vutrisiran during the RTE (patisiran/vutrisiran). The TTR reduction observed in patients in the patisiran/vutrisiran group was comparable to the TTR reduction observed in patients who received vutrisiran during both the 18-month treatment period and the RTE (vutrisiran/vutrisiran) (**Figure 3**).[2]

Figure 3. Mean (±SE) Percent Change from Baseline in Serum TTR During the RTE.[2]



Abbreviations: BL = baseline; D = day; M = month; RTE = randomized treatment extension; Q3M = every 3 months; Q6M = every 6 months; SE = standard error; TTR = transthyretin.
From Cauquil et al.[2]

EFFICACY RESULTS

Total Vutrisiran Group

The clinical efficacy endpoint results at Months 18 of the RTE period among the total vutrisiran group are presented in **Table 2**. Efficacy endpoints generally remained stable relative to RTE baseline at Month 18.[2]

Table 2. Change from RTE Baseline in Clinical Efficacy Endpoints at Month 18.[2]

Endpoint	Total Vutrisiran (N=149)
mNIS+7[a]	
RTE baseline, mean (SD)	58.4 (39.7), n=147
Change from RTE baseline at Month 18, mean (SE)	5.4 (1.4), n=130
Norfolk QOL-DN[b]	
RTE baseline, mean (SD)	42.9 (26.8), n=148
Change from RTE baseline at Month 18, mean (SE)	5.2 (1.5), n=131
10-MWT[c], m/s	
RTE baseline, mean (SD)	1.013 (0.472), n=148
Change from RTE baseline at Month 18, mean (SE)	-0.087 (0.018), n=131
mBMI, kg/m^2 x g/L	
RTE baseline, mean (SD)	1080.2 (235.6), n=147
Change from RTE baseline at Month 18, mean (SE)	-10.3 (8.4), n=128
R-ODS[d]	
RTE baseline, mean (SD)	33.8 (12.0), n=148

Endpoint	Total Vutrisiran (N=149)
Change from RTE baseline at Month 18, mean (SE)	-2.3 (0.4), n=132
PND score[e]	
RTE baseline, 0/1/11/IIIA/IIIB/IV, %	0.7/39.6/33.6/12.8/11.4/2.0, n=149
Change from RTE baseline at Month 18, disease stabilization/improvement/worsening, %[f]	67.8/5.4/18.1, n=136

Abbreviations: 10-MWT = 10-meter walk test; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life- Diabetic Neuropathy PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension; SD = standard deviation; SE = standard error.

[a]Mean of two non-missing assessments at the last scheduled efficacy assessment visit before the first dose of the RTE period or a single assessment score performed at the RTE visits after component imputation. Lower scores indicate less neurologic impairment (range: 0–304).

[b]Composite of 35 quality-of-life questions; lower scores indicate higher quality of life (range: –4 to 136).

[c]10 meters/mean time (seconds) taken to complete two assessments from the last scheduled efficacy assessment visit before the first dose of the RTE period; and single assessment performed at RTE months 9 and 18 visits. Imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.

[d]Composite of 24 disability questions; higher scores indicate lower disability (range: 0–48).

[e]PND score I: preserved walking, sensory disturbances; II: impaired walking but can walk without stick or crutch; III A: walk with one stick or crutch; III B: walk with two sticks or crutches; IV: confined to wheelchair or bedridden.

[f]Percentages are based on total number of patients (149); number of patients with assessments at each visit are indicated.

Switch from Patisiran to Vutrisiran

At Month 18 of the RTE period, a consistent clinical effect was observed across efficacy endpoints among patients who previously received patisiran during the 18-month treatment period and switched to vutrisiran (**Table 3**).[2]

Table 3. Change from Baseline for Select Clinical Efficacy Endpoints for Patients Who Switched From Patisiran to Vutrisiran During the RTE.[2]

Endpoint	Patients on Patisiran During the Treatment Period (n=42)	Patients on Vutrisiran During the Treatment Period and RTE (n=122)
mNIS+7[a]		
Study baseline, mean (SD)	57.7 (33.7), n=42	60.6 (36.0), n=122
Change from study baseline to end of 18-month treatment period, mean (SD)	1.6 (21.5), n=36	0.2 (13.9), n=112
Change from study baseline to RTE at Month 18, mean (SD)	3.7 (20.8), n=32	5.2 (21.0), n=98
Norfolk QOL-DN[b]		
Study baseline, mean (SD)	47.3 (29.9), n=42	47.1 (26.3), n=121
Change from study baseline to end of 18-month treatment period, mean (SD)	-0.6 (19.3), n=38	-2.4 (20.8), n=111
Change from study baseline to RTE at Month 18, mean (SD)	1.8 (19.3), n=32	4.1 (26.1), n=98
10-MWT[c], m/s		
Study baseline, mean (SD)	1.011 (0.400) n=42	1.006 (0.393), n=122
Change from study baseline to end of 18-month treatment period, mean (SD)	-0.043 (0.276), n=38	-0.016 (0.259), n=112
Change from study baseline to RTE at Month 18, mean (SD)	-0.092 (0.250), n=32	-0.058 (0.292), n=99
mBMI, kg/m^2 x g/L		
Study baseline, mean (SD)	1058.1 (228.8), n=42	1058.0 (233.0), n=122
Change from study baseline to end of 18-month treatment period, mean (SD)	6.9 (91.8), n=38	21.8 (101.1), n=113

Endpoint	Patients on Patisiran During the Treatment Period (n=42)	Patients on Vutrisiran During the Treatment Period and RTE (n=122)
Change from study baseline to RTE at Month 18, mean (SD)	26.8 (113.2), n=29	7.4 (112.2), n=99
R-ODS[d]		
Study baseline, mean (SD)	34.0 (10.4), n=42	34.1 (11.0), n=122
Change from study baseline to end of 18-month treatment period, mean (SD)	-1.2 (5.9), n=38	-1.2 (5.5), n=113
Change from study baseline to RTE at Month 18, mean (SD)	-3.0 (6.2), n=32	-3.2 (7.0), n=100
PND score[e], %		
Study baseline, 0/1/11/IIIA/IIIB/IV, %	0/35.7/40.5/16.7/7.1/0, n=42	0/36.1/41.0/13.1/9.8/0, n=122
Change from study baseline to end of 18-month treatment period, disease stabilization/improvement/worsening, %[f]	71.4/2.4/16.7, n=38	67.2/10.7/16.4 [115]
Change from study baseline to RTE at Month 18, disease stabilization/improvement/worsening, %[f]	61.9/0/16.7, n=33	51.6/7.4/25.4 [103]

Abbreviations: 10-MWT = 10-meter walk test; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; Norfolk QOL-DN = Norfolk Quality of Life- Diabetic Neuropathy; PND = polyneuropathy disability; R-ODS = Rasch-built Overall Disability Scale; RTE = randomized treatment extension; SD = standard deviation.

[a]Mean of two non-missing assessments at the last scheduled efficacy assessment visit before the first dose of the RTE period or a single assessment score performed at the RTE visits after component imputation. Lower scores indicate less neurologic impairment (range: 0–304).

[b]Composite of 35 quality-of-life questions; lower scores indicate higher quality of life (range: –4 to 136).

[c]10 meters/mean time (seconds) taken to complete two assessments from the last scheduled efficacy assessment visit before the first dose of the RTE period; and single assessment performed at RTE months 9 and 18 visits. Imputed as 0 for patients unable to perform the walk; higher speeds indicate greater ambulatory function.

[d]Composite of 24 disability questions; higher scores indicate lower disability (range: 0–48).

[e]PND score I: preserved walking, sensory disturbances; II: impaired walking but can walk without stick or crutch; III A: walk with one stick or crutch; III B: walk with two sticks or crutches; IV: confined to wheelchair or bedridden.

[f]Percentages are based on total number of patients (42 or 122); number of patients with assessments at each visit are indicated.

SAFETY RESULTS

The median treatment duration in the total vutrisiran group was 27.3 months (range: 0.7-44.6 months). The majority of AEs reported were mild or moderate in severity. A summary of the AEs observed during the RTE period compared with the 18-month treatment period are presented in **Table 4**.[2]

The most common AEs reported in ≥10% of patients in the total vutrisiran group were COVID-19 (31.5%), urinary tract infection (17.4%), and fall (14.8%). No SAEs were considered related to vutrisiran in the RTE. Twelve deaths were reported during the RTE period, and 1 additional death was reported after the patient had stopped participation in the study. None of the deaths were considered related to vutrisiran by investigators.[2,4]

There were no new safety concerns identified during the RTE period. The safety profile of vutrisiran was consistent with that observed previously in the treatment period of the HELIOS-A study.[2]

Table 4. AEs with Vutrisiran during the RTE (RTE Population) and 18-Month Treatment Period (Safety Population) of HELIOS-A, and with External Placebo from APOLLO.[2]

n (%)/ER (number of events per 100 PY)	HELIOS-A RTE	HELIOS-A 18-month treatment period	APOLLO
	Total Vutrisiran (N=149; PY=376.2)	Vutrisiran, 25 mg Q3M (n = 122; PY=191.3)	Placebo (n=77; PY=96.1)
Treatment duration, months, mean (range)	30.3 (0.7-44.6)	18.8 (1.7-19.4)	15.0 (1.3-18.8)
Any AE	139 (93.3)/291.6	119 (97.5)/552.6	75 (97.4)/1280.5
Treatment-related	10 (6.7)/6.9	29 (23.8)/33.5	30 (39.0)/197.6
AEs occurring in ≥10% of patients in the RTE			
COVID-19	47 (31.5)/13.6	4 (3.3)/2.6	0/0
Urinary tract infection	26 (17.4)/13.0	16 (13.1)/13.1	14 (18.2)/23.9
Fall	22 (14.8)/9.0	22 (18.0)/20.4	22 (28.6)/44.7
Severe AEs	51 (34.2)/30.3	19 (15.6)/20.9	28 (36.4)/91.5
SAE	59 (39.6)/40.4	32 (26.2)/32.9	31 (40.3)/103.0
AE leading to treatment discontinuation	11 (7.4)/2.9	3 (2.5)/1.6	11 (14.3)/15.6
AE leading to stopping study participation	11 (7.4)/2.9	3 (2.5)/1.6	9 (11.7)/11.4
Death[a]	13 (8.7)	2 (1.6)	6 (7.8)
SAE occurring in ≥2% of patients in the RTE			
Cellulitis	5 (3.4)/1.6	0/0	1 (1.3)/1.0
Pneumonia	3 (2.0)/0.8	3 (2.5)/2.1	3 (3.9)/3.1
Cardiac failure	3 (2.0)/0.8	1 (0.8)/0.5	2 (2.6)/2.1
Cardiac failure acute	3 (2.0)/0.8	1 (0.8)/1.0	1 (1.3)/2.1
Osteoarthritis	3 (2.0)/0.8	1 (0.8)/0.5	0/0
Cardiac disorders[b],AEs	34 (22.8)/16.2	37 (30.3)/34.0	28 (36.4)/46.8
Cardiac disorders[b], SAEs	17 (11.4)/6.1	11 (9.0)/8.9	10 (13.0)/15.6
Eye disorders[b,c], AEs	20 (13.4)/12.5	35 (28.7)/28.2	20 (26.0)/27.0

Abbreviations: AE = adverse event; ER = event rate; PY = patient-years; RTE = randomized treatment extension; SAE = serious adverse event.

[a]Includes death reported in 1 patient in the vutrisiran 25 mg group that occurred after the patient stopped study participation.

[b]System organ class.

[c]Eye disorders included vitreous opacities (n = 4), vitreous floaters, glaucoma and conjunctival hyperemia (all n = 3); ocular hypertension, visual impairment and vitreous detachment (all n = 2); age-related macular degeneration, blepharitis, cataract, conjunctival cyst, conjunctival hemorrhage, diplopia, dry eye, eye irritation, eye edema, eye pain, eye pruritus, posterior capsule opacification, retinal tear, vision blurred, vitreous disorder, vitreous hemorrhage and xerophthalmia (all n = 1).

ABBREVIATIONS

10-MWT = 10-meter walk test; AE = adverse event; BL = baseline; CI = confidence interval; D = day; FAP = familial amyloid polyneuropathy; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; H-L = Hodges-Lehmann; IV = intravenous; M = month; mBMI = modified body mass index; mNIS+7 = modified Neuropathy Impairment Score +7; 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; PND = polyneuropathy disability; PY = patient-years; Q3M = every 3 months; Q6M = every 6 months; RTE = randomized treatment extension; R-ODS = Rasch-built Overall Disability Scale; SAE = serious adverse event; SD = standard deviation; SE = standard error; TTR = transthyretin.

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