Effect of Patisiran on Polyneuropathy and Cardiomyopathy in Patients with hATTR Amyloidosis with V122I/T60A Variants: A Phase 4 Observational Study

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Author Disclosures for Dr. Raymond Comenzo

Conflict	Disclosures
Alnylam Pharmaceuticals	Principal investigator in clinical trials

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Background and Rationale

hATTR Amyloidosis, Also Known as ATTRv Amyloidosis

- A rare, underdiagnosed, rapidly progressive, debilitating, and fatal disease caused by variants in the transthyretin (TTR) gene[1–4]
- A multisystem disease that can include sensory, motor, and autonomic neuropathy, and cardiac manifestations[2,3,5]
- V122I and T60A variants are historically associated with cardiomyopathy,[6,7] yet evidence of a mixed phenotype is emerging[8,9]
  - T60A is particularly associated with poor prognosis, with worsening of disease leading to a median survival time of ~3.4 years after diagnosis[10]

Patisiran

- An RNAi therapeutic administered once every 3 weeks via intravenous infusion, which silences production of both variant and wild-type TTR[11]
- Patisiran was approved for the treatment of the polyneuropathy of hATTR amyloidosis based on the Phase 3, placebo-controlled APOLLO study[12]
  - Of the patients receiving patisiran in the APOLLO study, only 1/148 (0.7%) had a V122I variant and 12/148 (8.1%) had a T60A variant

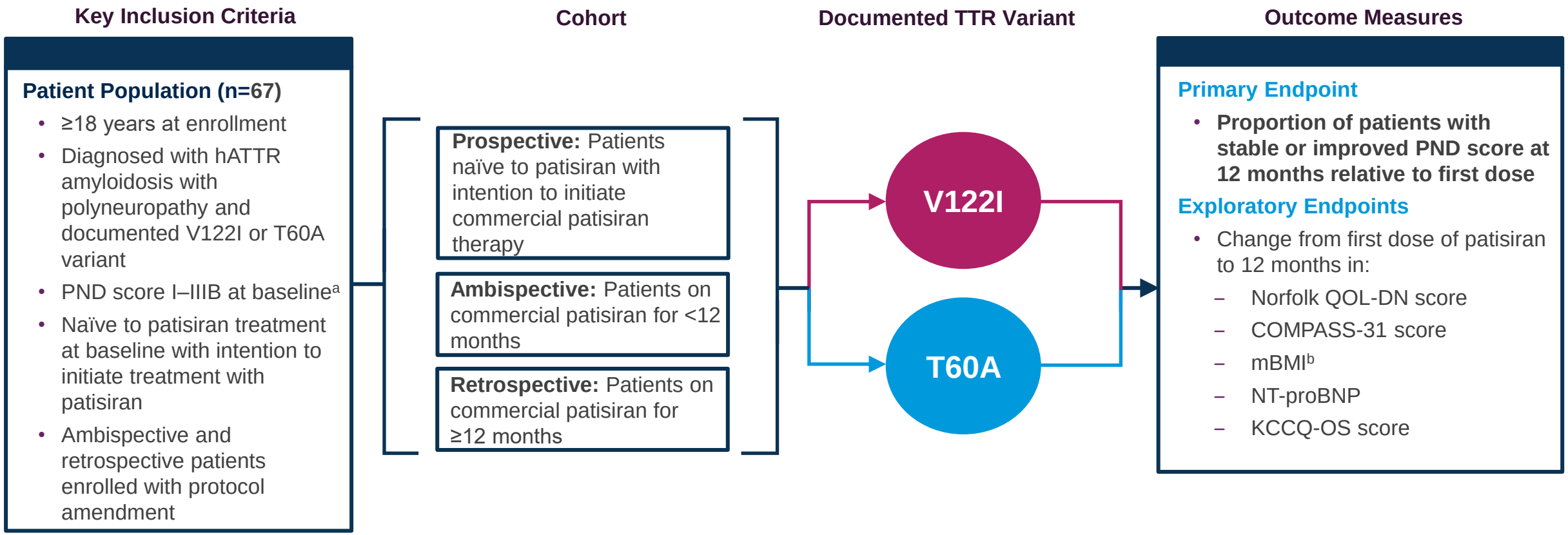
Objective

To evaluate the effectiveness of patisiran on ambulatory status in patients with hATTR amyloidosis with polyneuropathy and a V122I or T60A variant

ATTRv, hereditary transthyretin-mediated (v for variant); hATTR, hereditary transthyretin-mediated; RNAi, ribonucleic acid interference; TTR, transthyretin. 1. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 2. Hawkins et al. *Ann Med* 2015;47:625–38; 3. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 4. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 5. Benson et al. *Amyloid* 2018;25:215–9; 6. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 7. Ruberg et al. *Circulation* 2012;126:1286–300; 8. Hewitt et al. *J Cardiac Fail* 2020;26:S33; 9. Parker et al. *Sci Rep* 2021;11:11645; 10. Sattianayagam et al. *Eur J Heart Fail* 2012;33:1120–7. 11. Coelho et al. *N Engl J Med* 2013;369:819–29; 12. Adams et al. *N Engl J Med* 2018;379:11–21.

Phase 4 Study Design

- This multicenter, observational Phase 4 study enrolled patients in the USA with hATTR amyloidosis with polyneuropathy and a documented V122I or T60A variant into one of three cohorts (prospective, ambispective, retrospective) based on prior patisiran exposure



[a]Baseline, first dose of patisiran. [b]Albumin was collected as routine care, mBMI was calculated as BMI × albumin programmatically in the clinical database.
COMPASS-31, Composite Autonomic Symptom Scale 31-item Questionnaire; hATTR, hereditary transthyretin-mediated; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; mBMI, modified body mass index; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; PND, polyneuropathy disability; NT-proBNP, N-terminal prohormone of brain-type natriuretic peptide.

Baseline Demographics and Disease Characteristics (Safety Population[a])

- At baseline[b], patients experienced impaired quality of life and autonomic dysfunction, with a wide range of ambulatory dysfunction

Characteristic	V122I Variant (n=45)	T60A Variant (n=13)	Total (n=58)
Age[c], mean (range), years	66.1 (33–83)	61.3 (30–78)	65.1 (30–83)
Male, n (%)	30 (66.7)	7 (53.8)	37 (63.8)
Race[d], n (%)			
Black	36 (80.0)	0	36 (62.1)
White	8 (17.8)	13 (100.0)	21 (36.2)
Age at symptom onset/diagnosis, mean (range), years	61.8 (25–82)	57.0 (18–77)	60.7 (18–82)
Age at hATTR amyloidosis diagnosis, mean (range), years	64.6 (33–82)	59.3 (26–78)	63.4 (26–82)
Norfolk QOL-DN total score, mean (range)[e]	28.1 (–2 to 78)	37.0 (NA)	28.4 (–2 to 78)
COMPASS-31 total score, mean (range)[f]	22.6 (0–46)	18.3 (NA)	22.4 (0–46)
PND score, n (%)			
I: Preserved walking, sensory disturbances	26 (57.8)	7 (53.8)	33 (56.9)
II: Impaired walking, but can walk without stick/crutch	13 (28.9)	3 (23.1)	16 (27.6)
IIIA: Walk with 1 stick/crutch	3 (6.7)	2 (15.4)	5 (8.6)
IIIB: Walk with 2 sticks/crutches	3 (6.7)	1 (7.7)	4 (6.9)
KPS[g], n (%)			
100%	1 (2.2)	1 (7.7)	2 (3.4)
90%	8 (17.8)	5 (38.5)	13 (22.4)
80%	21 (46.7)	4 (30.8)	25 (43.1)
70%	13 (28.9)	2 (15.4)	15 (25.9)
60%	2 (4.4)	1 (7.7)	3 (5.2)
NYHA class[h], n (%)			
No heart failure	5 (11.1)	1 (7.7)	6 (10.3)
I	12 (26.7)	4 (30.8)	16 (27.6)
II	26 (57.8)	7 (53.8)	33 (56.9)
III	2 (4.4)	1 (7.7)	3 (5.2)

[a]All patients who received ≥1 dose of patisiran (n=58). [b]Baseline, first dose of patisiran. [c]Age was computed as informed consent year minus year of birth. [d]Race was "not reported" for one patient (V122I, 2.2%; total, 1.7%). [e]n=25 (V122I [n=24]); T60A (n=1). [f]n=23 (V122I [n=22]; T60A [n=1]). [g]Decreasing KPS indicates worsening performance status. [h]Patients with NYHA Class 4 heart failure at baseline were excluded from the study. COMPASS-31, Composite Autonomic Symptom Scale 31-item Questionnaire; hATTR, hereditary transthyretin-mediated; KPS, Karnofsky Performance Status; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NYHA, New York Heart Association; PND, polyneuropathy disability.

Relevant Surgical and Medical History (Safety Population[a])

- 22 (37.9%) had ≥1 relevant finding relating to hATTR amyloidosis in their surgical history
- Patients' past medical history indicated the presence of significant polyneuropathy

Relevant Surgical History

Category Preferred Term	V122I Variant (n=45)	T60A Variant (n=13)	Total (n=58)
≥1 relevant surgical history finding, n (%)	17 (37.8)	5 (38.5)	**22 (37.9)**
Cardiac surgery/intervention, n (%)	13 (28.9)	7 (53.8)	**15 (25.9)**
Pacemaker	4 (15.4[b])	1 (100.0[b])	5 (18.5[b])
Atrial Fibrillation	5 (11.1)	1 (7.7)	6 (10.3)
Other[c]	4 (8.9)	3 (23.1)	7 (12.1)
Orthopedic procedure, n (%)	8 (17.8)	2 (15.4)	**10 (17.2)**
Carpal tunnel decompression	4 (8.9)	1 (7.7)	5 (8.6)
Other[d]	7 (15.6)	1 (7.7)	8 (13.8)

Medical History Relevant to Polyneuropathy

System Organ Class[e] Preferred Term	V122I Variant (n=45)	T60A Variant (n=13)	Total (n=58)
Patients with a nervous system or cardiac disorder, n (%)	20 (44.4)	8 (61.5)	28 (48.3)
Patients with both nervous system and cardiac disorders, n (%)	9 (20.0)	1 (7.7)	10 (17.2)
Nervous system disorders, n (%)	16 (35.6)	4 (30.8)	20 (34.5)
Carpal tunnel syndrome	8 (17.8)	1 (7.7)	9 (15.5)
Neuropathy peripheral	4 (8.9)	0	4 (6.9)
Other[f]	10 (22.2)	4 (30.8)	14 (24.1)
Cardiac disorders[g], n (%)	13 (28.9)	5 (38.5)	18 (31.0)
Atrial fibrillation	5 (11.1)	1 (7.7)	6 (10.3)
Postural orthostatic tachycardia syndrome	1 (2.2)	0	1 (1.7)

[a]All patients who received ≥1 dose of patisiran (n=58). [b]These data are available from patients in the prospective cohort only (n=27; V122I [n=26]; T60A [n=1]), and percentages are calculated as such. [c]Ventricular tachycardia, atrioventricular block first degree, bundle branch block left, implantable defibrillator insertion, cardiac resynchronization therapy, and atrial appendage closure (n<5 for each condition). [d]Spinal laminectomy, spinal operation, hip arthroplasty, intervertebral disc operation, peripheral nerve decompression, rotator cuff repair (n<5 for each condition). [e]Data reported based on the MedDRA system organ class and preferred terms categorization. [f]Headache, lumbar radiculopathy, migraine, autonomic nervous system imbalance, cervical radiculopathy, dementia, embolic stroke, hypoesthesia, intercostal neuralgia, neuralgia, Parkinson's disease, restless legs syndrome, spinal cord compression, syncope, and transient ischemic attack (n<5 for each condition). [g]Cardiac disorders relevant to polyneuropathy include manifestations of cardiac autonomic neuropathy (ie. atrial fibrillation, orthostatic hypotension, resting tachycardia, neurocardiogenic syncope, postural orthostatic tachycardia syndrome). Cardiac disorders unrelated to polyneuropathy are not shown.
hATTR, hereditary transthyretin-mediated.

Primary Endpoint: PND Score at Month 12 Relative to First Dose of Patisiran

- 42/45 (93.3%) patients demonstrated stabilization or improvement in PND score from baseline to Month 12 of patisiran treatment
- Of the 3 patients who worsened, 2 had diabetes and 1 had small-fiber neuropathy associated with Ehlers–Danlos syndrome

PND Score at Baseline[a]	PND Score at Month 12[b,c]				
	0	I	II	IIIA	IIIB
I: Preserved walking, sensory disturbances	**4**	**20**	**2**	0	0
II: Impaired walking, but can walk without stick/crutch	0	**7**	**6**	**1**	0
IIIA: Walk with 1 stick/crutch	0	0	**1**	**2**	0
IIIB: Walk with 2 sticks/crutches	0	0	0	**1**	**1**

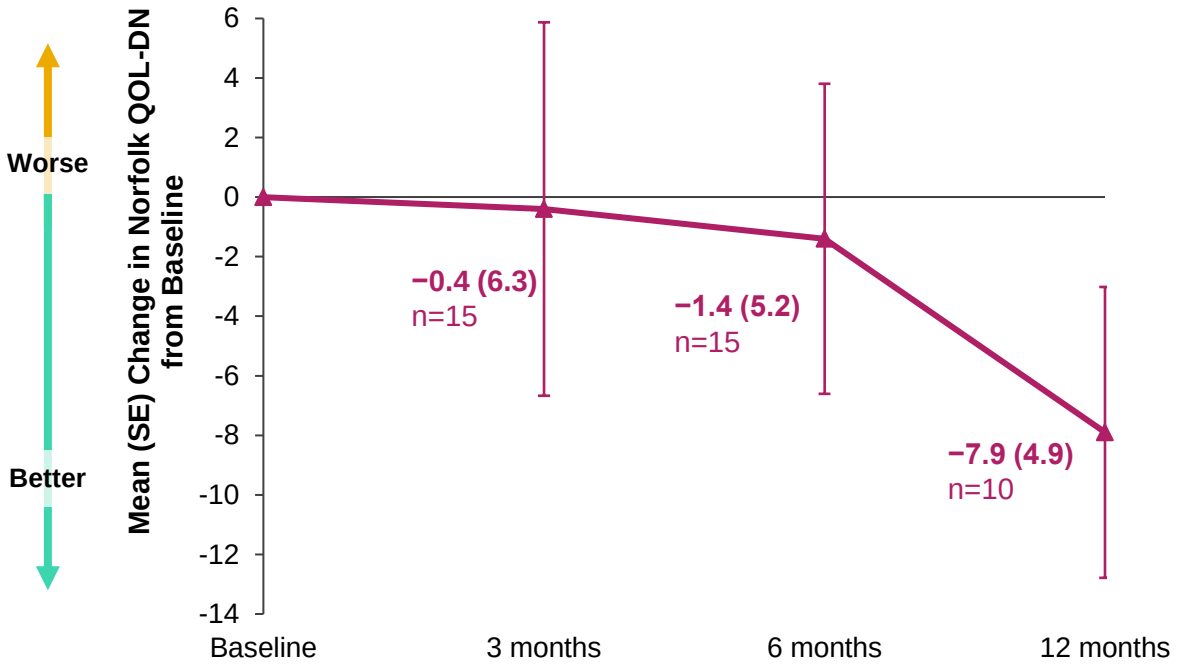
Improved (n=13, 28.9%) Stabilized (n=29, 64.4%) Worsened (n=3, 6.7%)

[a]Baseline, first dose of patisiran. [b]Analysis performed in the efficacy population, defined as all patients who completed 12 months of patisiran treatment (n=45). [C]The number of patients achieving the score is shown. In the V122I population (n=32), 13 patients (40.6%) improved, 17 (53.1%) stabilized, and 2 (6.3%) worsened. In the T60A population (n=13), no patients improved, 12 (92.3%) stabilized, and 1 (7.7%) worsened.
PND, polyneuropathy disability

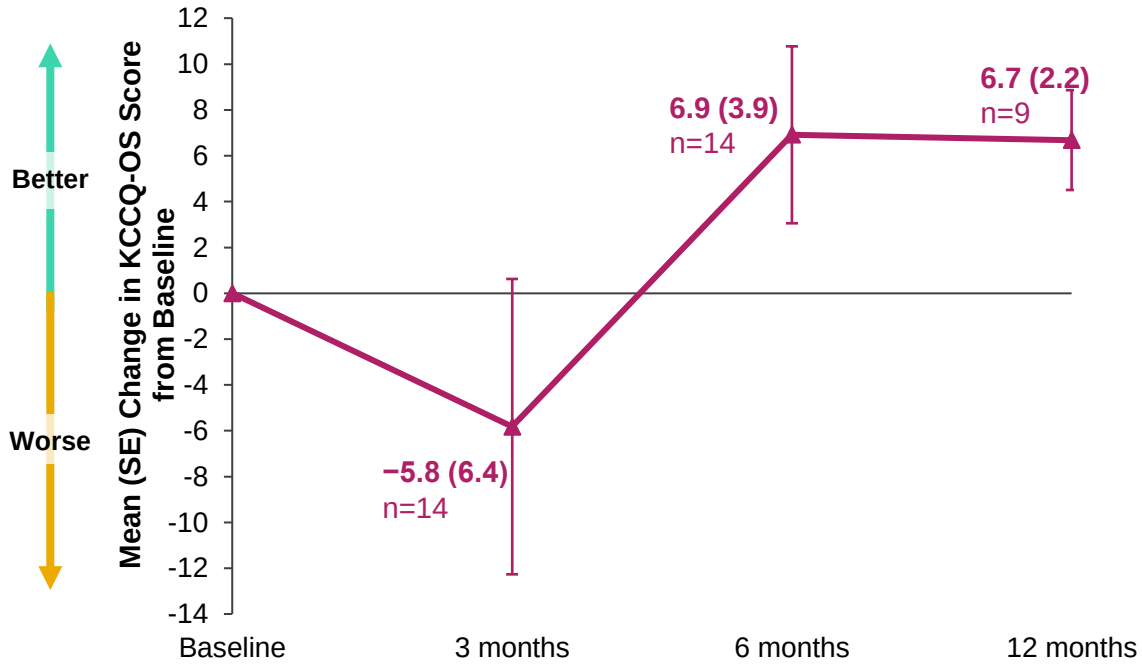
Exploratory Endpoints: Health-Related Quality of Life and Health Status

- Patients demonstrated an improvement in Norfolk QOL-DN from baseline to Month 12 of patisiran treatment, with the trend toward improvement evident as early as Month 3
- Patients demonstrated an improvement in KCCQ-OS from baseline, starting at Month 6 of patisiran

Change from Baseline to Month 12 in Norfolk QOL-DN Total Score[a,b]



Change from Baseline to Month 12 in KCCQ-OS[a,c]

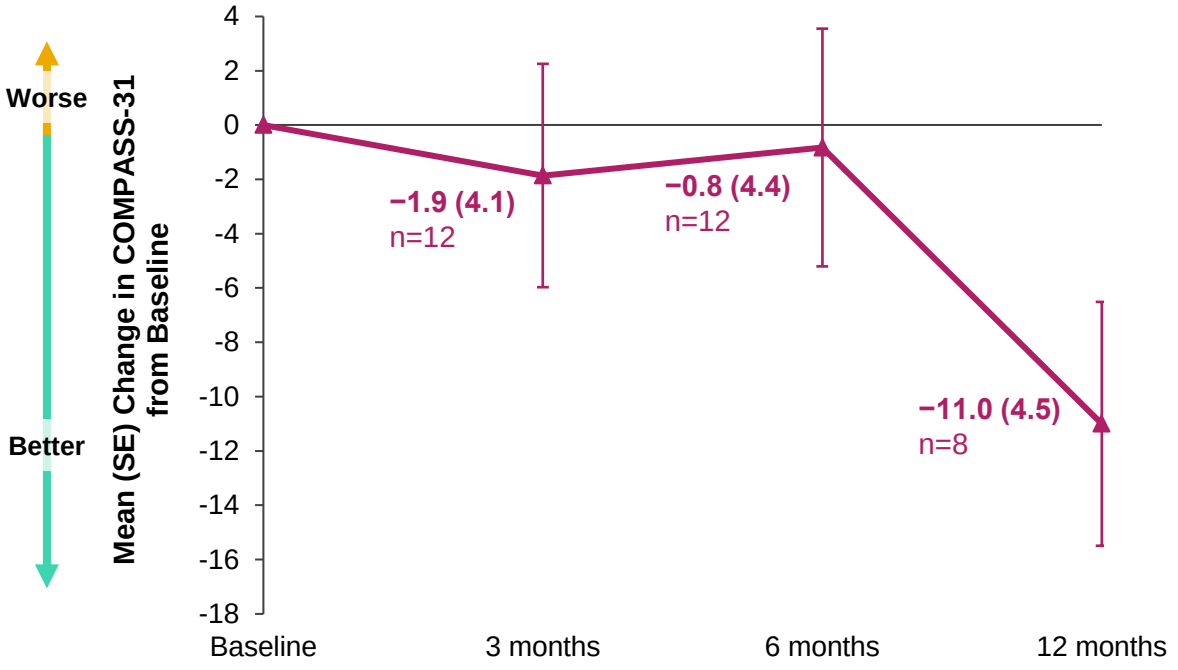


[a]Analysis performed in the efficacy population, defined as all patients who completed 12 months of patisiran treatment (n=45). [b]Mean (SE) Norfolk QOL-DN score at baseline was 28.44 (5.08), with a range of −2.0 to 78.0. Higher scores of Norfolk QOL-DN indicate worse QOL (range: −4 to 136). [c]Mean (SE) KCCQ-OS score at baseline was 63.97 (5.22). Lower KCCQ-OS scores indicate worse health status (range: 0–100).
KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SE, standard error.

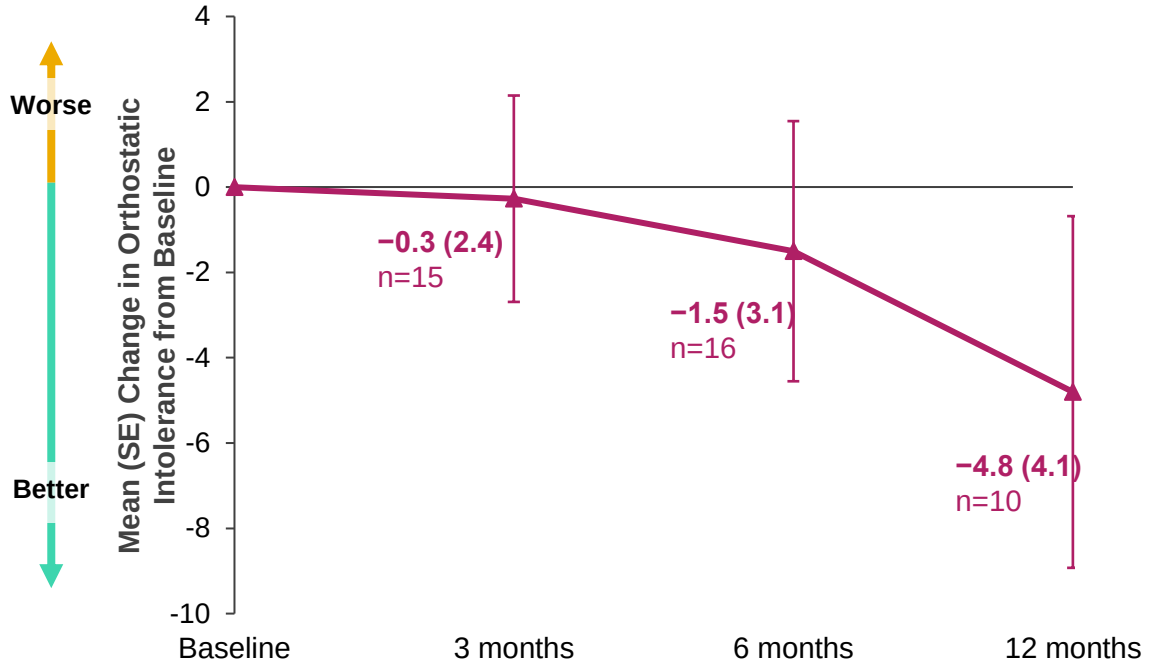
Exploratory Endpoints: Autonomic Symptoms and Nutritional Status

- Patients demonstrated improvements in COMPASS-31 and orthostatic intolerance from baseline to Month 12 of patisiran treatment
- Nutritional status, measured by modified body mass index, improved from baseline to Month 6 of patisiran treatment, and this improvement was maintained to Month 12
  - Mean [SE] change from baseline: Month 6, +118.9 [105.9] (n=6); Month 12, +201.8 [139.0] (n=5)

Change from Baseline to Month 12 in COMPASS-31 Total Score[a,b]



Change from Baseline to Month 12 in Orthostatic Intolerance[a,c]



[a]Analysis performed in the efficacy population, defined as all patients who completed 12 months of patisiran treatment (n=45). [b]Mean (SE) COMPASS-31 score at baseline was 22.40 (3.09), with a range of 0.0–45.7
[c]Orthostatic intolerance is a domain of COMPASS-31. Mean (SE) orthostatic intolerance score at baseline was 9.38 (1.93), with a range of 0.0–32.0. Higher scores of COMPASS-31 total (range: 0–100) and orthostatic intolerance (range: 0–40) indicate worse autonomic symptoms.
COMPASS-31, Composite Autonomic Symptom Scale 31-item Questionnaire; SE, standard error.

Safety

- 11 patients were hospitalized during the study
  - 4 of the 11 hospitalizations were associated with congestive heart failure
  - 3 of the 11 hospitalized patients subsequently died
  - All hospitalizations and deaths were unrelated to patisiran

Selected Safety Event	Patients with Event (n=42)[a]	Patient-Years of Exposure	Exposure-Adjusted Incidence Rate (Rate/Patient-Year)
≥1 serious treatment-emergent AE[b]	9	25.19	0.357
≥1 severe treatment-emergent AE[b]	8	25.19	0.318
≥1 treatment-emergent AE leading to study withdrawal[b]	2	25.19	0.079
Death[c]	4	25.19	0.159

The most common treatment-emergent AE was infusion-related reaction (n=2). Selected safety event includes events occurring or worsening on or after the first dose of patisiran are reported. Selected safety event includes death, SAEs, significant AEs that led to an intervention, marked laboratory abnormalities, overdose, pregnancy, and ADR. Selected safety events with missing causality are considered related. Selected safety events with missing severity are considered severe. [a]Patients in the prospective cohort and mixed cohort are summarized. [b]AEs considered unrelated to the study drug. [c]All deaths are reported as serious selected safety events, including those not treatment-emergent. Causes of death were: acute respiratory failure (n=1), exacerbation of heart failure not otherwise specified (n=1), cardiogenic shock (n=1), unknown (died at home, n=1). All deaths were considered unrelated to patisiran.
ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event.

Summary

- In this patisiran Phase 4 study, patients with a V122I or T60A variant of hATTR amyloidosis, historically associated with cardiomyopathy, also experienced polyneuropathy at baseline, as demonstrated by impaired quality of life, autonomic dysfunction, and a wide range of ambulatory dysfunction

- The primary endpoint of the study was met and 93.3% of patients demonstrated stabilization or improvement from baseline in PND score after 12 months of patisiran treatment

- Patients also demonstrated evidence of improvement from baseline in quality of life, autonomic symptoms, and health status after 12 months of patisiran treatment

- The safety profile of patisiran in treatment of hATTR amyloidosis with polyneuropathy in patients with a V122I or T60A variant was acceptable and consistent with previously known data from clinical trial and post-marketing experience

hATTR, hereditary transthyretin-mediated; PND, polyneuropathy disability.

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the Phase 4 study, especially considering the challenges of continuing the study during the COVID-19 pandemic