Effect of Patisiran on Polyneuropathy and Cardiomyopathy in Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis with a V122I or T60A Variant: A Phase 4 Observational Study

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Summary

- **In this patisiran Phase 4 study, patients with a V122I or T60A variant of hereditary transthyretin-mediated (hATTR) amyloidosis, historically associated with cardiomyopathy, also experienced polyneuropathy at baseline, as demonstrated by impaired quality of life (QOL), 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 polyneuropathy disability (PND) score after 12 months of patisiran treatment**
- **Patients also demonstrated evidence of improvement from baseline in QOL, autonomic symptoms, and health status after 12 months of patisiran treatment**
- **Patisiran demonstrated an acceptable safety profile, consistent with existing data**

Introduction

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

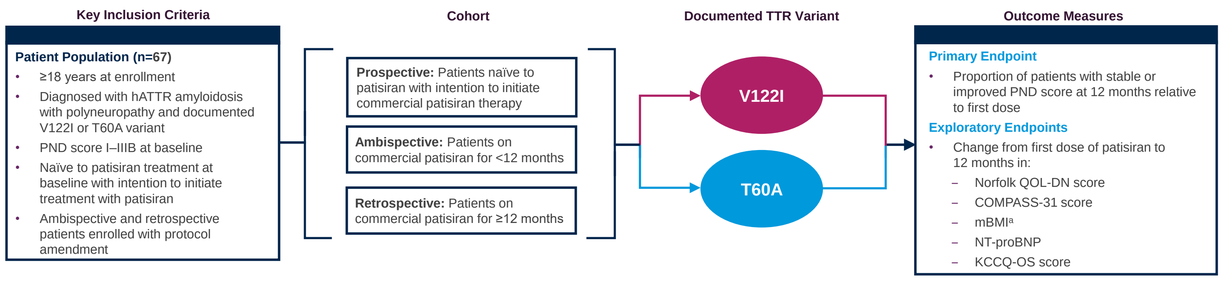
- To evaluate the effectiveness of patisiran on ambulatory status in patients with hATTR amyloidosis with polyneuropathy and a V122I or T60A variant

Methods

Study Design

- This multicenter, observational, Phase 4 study (NCT04201418) enrolled patients in the USA with hATTR amyloidosis with polyneuropathy and a documented V122I or T60A variant
- Patients were enrolled into one of three cohorts (prospective, ambispective, retrospective) based on prior patisiran exposure (**Figure 1**)
- The primary endpoint was proportion of patients with stable or improved polyneuropathy disability (PND) score after 12 months of patisiran treatment relative to first dose

Figure 1. Patisiran Phase 4 Study Design



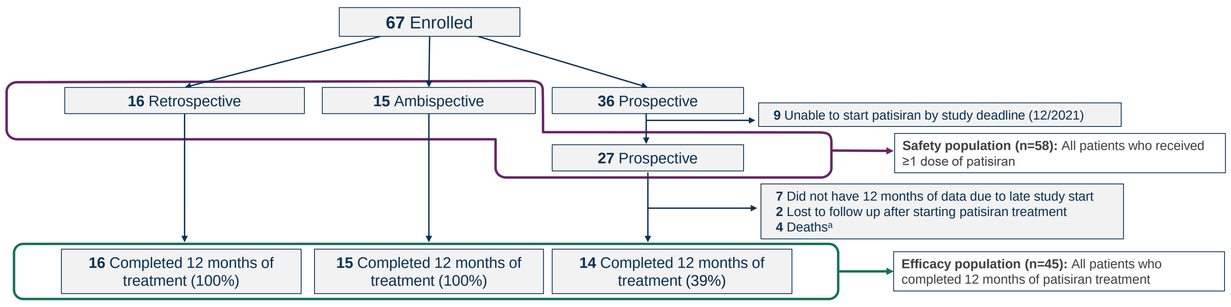
[a]If albumin was collected as routine care, mBMI was calculated as BMI × albumin programmatically in the clinical database

Results

Baseline Demographics and Treatment

- 67 patients enrolled in the study; 58 patients constituted the safety population and 45 patients constituted the efficacy population (**Figure 2**)
- On average, patients experienced a delay in hATTR amyloidosis diagnosis of 2.7 years after initial symptom onset **(Table 1)**
  - 32 (55.1%) patients were diagnosed by the presence of TTR amyloid in extracardiac sites, highlighting the presence of multisystem disease
- Of the 58 patients in the safety population, the majority (50 [86.2%]) enrolled in the study due to disease progression
  - 20 (34.5%) patients experienced both cardiac and neuropathic progression, while 26 (44.8%) patients experienced neuropathic progression only
  - 7 (12.1%) patients enrolled in the study due to the potential clinical benefit of patisiran; although symptomatic, these patients had not yet experienced disease progression
- 26 (44.8%) were being treated with a TTR stabilizer (19 [32.8%] tafamidis, 8 [13.8%] diflunisal) during the study, concurrently with patisiran[d] (**Table 1**)

Figure 2. Phase 4 Patient Disposition



[a]Deaths unrelated to patisiran: 1 acute respiratory failure, 1 exacerbation of heart failure not otherwise specified, 1 unknown cause (died at home), 1 cardiogenic shock

Table 1. Baseline Demographics (Safety Population)

Characteristic	V122I Variant (n=45)	T60A Variant (n=13)	Total (n=58)
Mean age[a], 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, n (%)			
Black	36 (80.0)	0	36 (62.1)
White	8 (17.8)	13 (100.0)	21 (36.2)
Not reported	1 (2.2)	0	1 (1.7)
Mean age at hATTR amyloidosis symptom onset, mean (range), years	61.8 (25–82)	57.0 (18–77)	60.7 (18–82)
Mean age at hATTR amyloidosis diagnosis, mean (range), years	64.6 (33–82)	59.3 (26–78)	63.4 (26–82)
Method of confirming diagnosis[b], n (%)			
Technetium scan	20 (44.4)	4 (30.8)	24 (41.4)
Cardiac biopsy	5 (11.1)	1 (7.7)	6 (10.3)
Fat pad biopsy	1 (2.2)	5 (38.5)	6 (10.3)
Salivary gland biopsy	3 (6.7)	0	3 (5.2)
Sural nerve biopsy	0	3 (23.1)	3 (5.2)
Other biopsy[c]	18 (40.0)	5 (38.5)	23 (39.7)
hATTR amyloidosis treatment received concurrently with patisiran, n (%)			
Yes[d]	18 (40.0)	8 (61.5)	26 (44.8)
Tafamidis[e]	13 (28.9)	6 (46.2)	19 (32.8)
Diflunisal[f]	5 (11.1)	3 (23.1)	8 (13.8)
Doxycycline	3 (6.7)	2 (15.4)	5 (8.6)
Inotersen	0	0	0
TUDCA	0	1 (7.7)	1 (1.7)
Other[g]	1 (2.2)	1 (7.7)	2 (3.4)
No	27 (60.0)	5 (38.5)	32 (55.2)

[a]Age was computed as informed consent year minus year of birth. [b]Some patients' diagnosis was confirmed by >1 method, so percentages do not sum to 100%. [c]Other includes: skin biopsy (6); *TTR* DNA sequencing by blood (3); blood (1); bone marrow (2); muscle (2); duodenum, gastric antrum, proximal esophagus (1); Invitae genetic testing laboratory panel (1); kidney, lung (1); lung (1); MRI (1); rectal biopsy (1); gastric mucosa (1); sigmoid colon (1); *TTR* genetic analysis and skin biopsy (1). [d]Patients could take >1 medication, so percentages do not sum to 100%. [e]15 patients receiving tafamidis (93.8%) initiated patisiran treatment due to neuropathy progression. [f]6 patients on diflunisal (75.0%) initiated patisiran treatment due to neuropathy progression. [g]Ursodiol, green tea extract

Table 2. Baseline Disease Characteristics (Safety Population)

Characteristic	V122I Variant (n=45)	T60A Variant (n=13)	Total (n=58)
Norfolk QOL-DN total score, mean (range)[a]	28.1 (–2 to 78)	37.0 (NA)	28.4 (–2 to 78)
COMPASS-31 total score, mean (range)[b]	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[c], 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[d], 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]n=25 (V122I [n=24]; T60A [n=1]. [b]n=23 (V122I [n=22]; T60A [n=1]). [c]Decreasing KPS indicates worsening performance status. [d]Patients with NYHA Class 4 heart failure at baseline were excluded from the study

Results (cont.)

Baseline Disease Characteristics (Table 2)

- At study baseline, patients experienced impaired QOL (mean [range] Norfolk Quality of Life-Diabetic Neuropathy [QOL-DN] questionnaire, 28.4 [–2 to 78]) and autonomic dysfunction (mean [range] Composite Autonomic Symptom Scale 31-item Questionnaire [COMPASS-31], 22.4 [0–46])
- Patients experienced a wide range of ambulatory dysfunction, with 33 (56.9%) patients having a PND score of I, 16 (27.6%) with a PND score of II, and 9 (15.5%) with a PND score of IIIA/B
  - 25 (43.1%) patients experienced impaired ambulation (PND II–IIIB) at study entry
- The majority of patients (43 [74.1%]) experienced decreased performance status, as indicated by Karnofsky Performance Status 60–80%
- 22 (37.9%) patients had few (New York Heart Association Class I) or no heart failure symptoms

Relevant Surgical and Medical History

- 22 (37.9%) patients had at ≥1 relevant finding relating to hATTR amyloidosis in their surgical history (**Table 3**)
  - 15 (25.9%) patients underwent intervention related to underlying arrhythmia that may be associated with autonomic dysfunction as a manifestation of hATTR amyloidosis
  - 10 (17.2%) patients underwent orthopedic procedures related to amyloid deposition in their musculoskeletal, connective, and soft tissues
- Patients' past medical history indicated the presence of significant polyneuropathy, including autonomic and sensory/motor dysfunction (**Table 4**)

Table 3. Relevant Surgical History (Safety Population)

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[a])	1 (100.0[a])	5 (18.5[a])
Atrial Fibrillation	5 (11.1)	1 (7.7)	6 (10.3)
Other[b]	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[c]	7 (15.6)	1 (7.7)	8 (13.8)

[a]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. [b]Ventricular tachycardia, atrioventricular block first degree, bundle branch block left, implantable defibrillator insertion, cardiac resynchronisation therapy, and atrial appendage closure (n<5 for each condition). [c]Spinal laminectomy, spinal operation, hip arthroplasty, intervertebral disc operation, peripheral nerve decompression, rotator cuff repair (n<5 for each condition)

Table 4. Medical History Relevant to Polyneuropathy (Safety Population)

System Organ Class 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[a]	10 (22.2)	4 (30.8)	14 (24.1)
Cardiac disorders[b], 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)

Data reported based on the MedDRA system organ class and preferred terms categorization
[a]Headache, lumbar radiculopathy, migraine, autonomic nervous system imbalance, cervical radiculopathy, dementia, embolic stroke, hypoaesthesia, intercostal neuralgia, neuralgia, Parkinson's disease, restless legs syndrome, spinal cord compression, syncope, and transient ischaemic attack (n<5 for each condition). [b]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

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 (**Table 5**)
- Of the 3 patients that worsened, 2 had diabetes and 1 had small-fiber neuropathy associated with Ehlers–Danlos syndrome

Table 5. PND Score from Baseline to Month 12 (Efficacy Population)

PND Score at Baseline	PND Score at Month 12[a] 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**

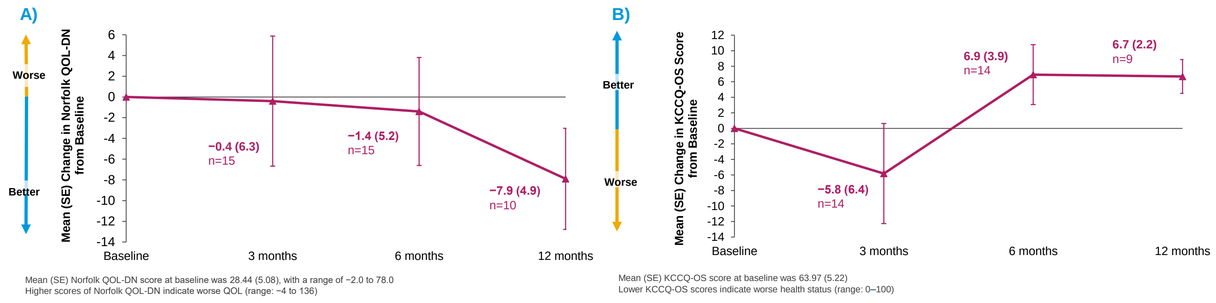
Improved (n=13, 28.9%) Stabilized (n=29, 64.4%) Worsened (n=3, 6.7%)

[a]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.

Exploratory Endpoints: Health-Related Quality of Life, Health Status, Autonomic, and Nutritional Status Measures

- Patients demonstrated an improvement in Norfolk QOL-DN from baseline to Month 12 of patisiran treatment, with the trend towards improvement evident as early as Month 3 (**Figure 3A**)
- Patients demonstrated an improvement in KCCQ-OS from baseline, starting at Month 6 of patisiran treatment (**Figure 3B**)
- Patients demonstrated improvements in COMPASS-31 and orthostatic intolerance[a] from baseline to Month 12 of patisiran treatment (**Figure 4**)

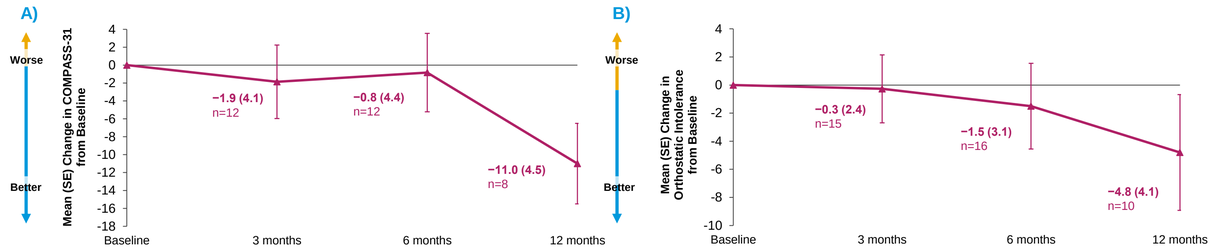
Figure 3. Mean (SE) Change from Baseline to Month 12 in A) Norfolk QOL-DN Total Score, B) KCCQ-OS Score in Patisiran-Treated Patients (Efficacy Population)



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)

Mean (SE) KCCQ-OS score at baseline was 63.97 (5.22)
Lower KCCQ-OS scores indicate worse health status (range: 0–100)

Figure 4. Mean (SE) Change from Baseline to Month 12 in A) COMPASS-31 Total Score, B) Orthostatic Intolerance[a] in Patisiran-Treated Patients (Efficacy Population)



Mean (SE) COMPASS-31 score at baseline was 22.40 (3.09), with a range of 0.0–45.7. 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
[a]Orthostatic intolerance is a domain of COMPASS-31

- 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)

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

Table 6. Overall Summary of Selected Safety Events

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

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