Neurol Ther
https://doi.org/10.1007/s40120-022-00414-z

ORIGINAL RESEARCH

Characteristics of Patients with Hereditary Transthyretin Amyloidosis-Polyneuropathy (ATTRv-PN) in NEURO-TTRansform, an Open-label Phase 3 Study of Eplontersen

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Received: August 25, 2022 / Accepted: October 17, 2022

ABSTRACT

Introduction: Hereditary transthyretin (ATTRv) amyloidosis is a rare, severe, progressive, debilitating, and ultimately fatal disease caused by systemic deposition of transthyretin (TTR) amyloid fibrils. ATTRv amyloidosis occurs in both males and females. Eplontersen (ION-682884), a ligand-conjugated antisense oligonucleotide designed to degrade hepatic *TTR* mRNA, is being evaluated for the treatment of ATTRv amyloidosis with polyneuropathy (ATTRv-PN) in the phase 3, international, multicenter, open-label NEURO-TTRansform study (NCT04136184). To describe the study population of this pivotal trial, here we report the baseline characteristics of patients enrolled in the NEURO-TTRansform study.

Methods: Patients eligible for NEURO-TTRansform were 18–82 years old with a diagnosis of ATTRv-PN and Coutinho stage 1 (ambulatory without assistance) or stage 2 (ambulatory with assistance) disease; documented *TTR* gene variant; signs and symptoms consistent with neuropathy associated with ATTRv; no prior liver transplant; and New York Heart Association (NYHA) functional class I or II.

Results: The NEURO-TTRansform study enrolled 168 patients across 15 countries/territories (North America, 15.5%; Europe, 38.1%; South America/Australia/Asia, 46.4%). At baseline, the study cohort had a mean age of 52.8 years, 69.0% of patients were male, and 78.0% of patients were White. The V30M variant was most prevalent (60.1% of patients), and prevalence varied by region. Overall, 56.5% and 17.3% of patients had received previous treatment with tafamidis or diflunisal, respectively. A majority of patients (79.2%) had Coutinho stage 1 disease (unimpaired ambulation) and early (before age 50) disease onset (53.0%). Time from diagnosis to enrollment was 46.6 (57.4) months (mean [standard deviation]). Most patients had a baseline polyneuropathy disability (PND) score of I (40.5%) or II (41.1%), and the mean modified Neuropathy Impairment Score + 7 (mNIS + 7) was 79.0.

Conclusion: The recruited population in the ongoing NEURO-TTRansform study has global representation characteristic of contemporary clinical practice.

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Published online: 16 December 2022

Trial Registration: ClinicalTrials.gov identifier NCT04136184.

PLAIN LANGUAGE SUMMARY

Hereditary transthyretin amyloidosis, also called ATTRv amyloidosis, is a rare and serious disease that is passed down within families. People with ATTRv amyloidosis have a genetic variant that causes their liver to make abnormal versions of the transthyretin protein (also known as "TTR"), which clump together into "clusters" called amyloids. The amyloid clusters build up in various body tissues and organs such as the liver, nerves, heart, and kidney, causing damage that could ultimately lead to death. ATTRv amyloidosis is a progressive disease, meaning that it gets worse over time. Liver transplant has traditionally been the only treatment option. Recently, drugs that target TTR have been approved by the FDA, and potential drugs are being tested in clinical trials. Eplontersen is designed to degrade *TTR* mRNA in the liver and inhibit the production of TTR protein. NEURO-TTRansform is a global phase 3 study investigating the effectiveness and safety of eplontersen in 168 adults with ATTRv amyloidosis with polyneuropathy (ATTRv-PN), a disease in which amyloid accumulation in peripheral nerves causes multisystem damage and eventually death. This scientific article describes the characteristics of the patients at enrollment, including age, gender, geographic location, and disease-related information, to help improve the understanding of ATTRv-PN. NEURO-TTRansform is an ongoing study, and the results will be published at a later time as prespecified in the analysis plan.

Keywords: Amyloid; ATTR; Cardiomyopathy; Eplontersen; Polyneuropathy; Transthyretin amyloidosis

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Key Summary Points

Why carry out this study?

ATTRv-PN is a highly debilitating and ultimately fatal disease, with considerable quality-of-life (QoL) burdens for patients and caregivers

Diagnosis is hindered by the rarity of the disease and nonspecific presenting symptoms, yet early identification and treatment are critical to preserve multisystem function and improve QoL outcomes

The data presented in this paper characterize the population of a pivotal phase 3 trial in ATTRv-PN and contribute to understanding of this rare population

What was learned from the study?

The baseline characteristics of the ongoing, fully enrolled phase 3 NEURO-TTRansform trial reveal a diverse population of patients with a wide range of regional, genetic, and disease-severity attributes

The study population is reflective of patients with ATTRv-PN encountered globally in clinical practice

INTRODUCTION

Hereditary transthyretin (TTR) amyloidosis with polyneuropathy (ATTRv-PN; v for "variant") is a rare, debilitating, and ultimately fatal disease involving progressive peripheral nerve damage [1–3]. Recent data suggest the global prevalence of ATTRv-PN is between 5500 and 38,500 persons [4]. In the same analysis [4], the prevalence of ATTRv-PN in the US was extrapolated to range from 104 to 2488 individuals; however, this estimate assumed penetrance among Caucasians only, and the true prevalence is likely much higher. ATTRv-PN is considered endemic to Portugal, Sweden, and certain regions in Japan, but has been increasingly reported in multiple countries worldwide [4].

The underlying pathophysiology of ATTRv-PN most frequently stems from single-point mutations in the *TTR* gene (inheritance is autosomal dominant with incomplete penetrance) [1]. The resulting abnormal, misfolded TTR proteins form amyloid deposits in peripheral and autonomic nerves and major organs, including the heart, gastrointestinal tract, kidneys, and eyes [3–5]. The predominant clinical consequences are progressive axonal sensorimotor and autonomic polyneuropathy (ATTRv-PN; historically, "familial amyloid polyneuropathy" or FAP) or cardiomyopathy (ATTRv-CM; historically, "familial amyloid cardiomyopathy" or FAC); however, mixed phenotype is common [6]. Death usually ensues within 6 to 12 years after symptom onset [1]. There are > 140 known genetic mutations associated with ATTRv amyloidosis [7], with wide variation in regional distribution and clinical expression of the different mutations [8, 9].

Due to progressive nerve injury, ATTRv-PN poses significant quality-of-life (QoL) burdens for both patients and their caregivers [9–11]. Early identification and treatment of ATTRv-PN are critical to preserve neuromuscular function and improve QoL outcomes. Diagnosis can be difficult, especially in nonendemic areas, given the rarity of the disease, heterogeneity of organ involvement, and nonspecific nature of many of the common presenting symptoms (e.g., pain, foot paresthesia and numbness, digestive disorders, erectile dysfunction, fatigue, weight loss, and plantar ulcers) [1, 3]. A constellation of symptoms, including progressive symmetric sensorimotor neuropathy combined with one or more of the following "red flag" symptoms should raise suspicion for ATTRv-PN: family history of neuropathy, early autonomic dysfunction (e.g., erectile dysfunction or postural hypotension), gastrointestinal complaints, unexplained weight loss, cardiac abnormalities (e.g., hypertrophy, arrhythmias, ventricular blocks, cardiomyopathy), bilateral carpal tunnel syndrome, renal abnormalities (e.g., albuminuria, mild azotemia), or vitreous opacities. Rapid neurologic progression distinguishes

ATTRv-PN from diabetic polyneuropathy [3]. Patients with early-onset disease (before age 50) almost always have a family history of neuropathy or cardiomyopathy [1]. A multisystem pattern of disease involvement is another important diagnostic indicator [6].

Eplontersen (formerly ION-682884; Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA) is an investigational *N*-acetyl galactosamine (GalNAc)-conjugated antisense oligonucleotide (ASO) that preferentially targets hepatic *TTR* mRNA, thereby inhibiting TTR protein synthesis [2]. In a phase 1 study in healthy volunteers, administration of eplontersen 45 mg SC every 4 weeks for a total of 4 doses ($n = 10$) achieved a mean reduction of 86% in serum TTR compared with baseline; there was a mean reduction of 6% in study participants administered placebo ($n = 6$) [12]. Subsequently, a phase 3 study, NEURO-TTRansform, was initiated to evaluate the efficacy and safety of eplontersen in adults with ATTRv-PN, all of whom had a documented pathogenic TTR sequence variant. The accessibility to such a sizable international cohort of patients with this rare disease provided a valuable opportunity to examine patient demographics, disease characteristics, and the variance of disease expression worldwide. Here, we report an analysis of the baseline characteristics of patients enrolled in the ongoing NEURO-TTRansform trial, with the objective of furthering understanding of the disease and its manifestations, thereby improving diagnostic aptitude. Safety and efficacy findings from NEURO-TTRansform will be published separately as they become available.

METHODS

Trial Design and Oversight

NEURO-TTRansform (NCT04136184; EudraCT: 2019-001698-10) is an international, open-label, phase 3 study conducted at 45 sites; the first patient enrolled on December 11, 2019. The study was designed to assess the efficacy and safety of eplontersen in patients with Coutinho stage 1 or stage 2 ATTRv-PN. The protocol was approved by the institutional review board at the study sites or an independent ethics committee, and trial conduct complied with the Declaration of Helsinki of 1964 and its later amendments and the Good Clinical Practice guidelines. Written informed consent was obtained for all patients prior to enrollment. Details of study design and rationale have been published elsewhere [2].

Patients

The study enrolled adults 18–82 years of age with a diagnosis of ATTRv-PN and meeting all of the following criteria: Coutinho stage 1 (ambulatory without assistance) or stage 2 (ambulatory with assistance) disease, a documented TTR sequence variant, and signs and symptoms consistent with neuropathy associated with ATTRv amyloidosis (including a Neuropathy Impairment Score [NIS] ≥ 10 and ≤ 130). Major exclusion criteria included: prior liver transplant; New York Heart Association (NYHA) functional classification $\geq$ III; alternative causes of polyneuropathy; current or previous treatment with inotersen, patisiran, ASOs, or gene-silencing small interfering ribonucleic acid (siRNA) drugs; current treatment (previous treatment must have been discontinued ≥ 2 weeks prior to study Day 1) with tafamidis, diflunisal, or doxycycline (alone or in combination with tauroursodeoxycholic acid); abnormal laboratory results including urine protein to creatinine ratio ≥ 1000 mg/g, platelets $< 125 \times 10^9$/l, or estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation ($eGFR_{creat\text{-}cys}$) [13] < 45 ml/min/1.73 m^2.

Baseline Data Collected

Data collected at screening/baseline included demographic information, geographic location by country/territory, TTR sequence variant (genotyping conducted if previous results not already available), disease history including previous treatment and clinical diagnosis of ATTRv-CM in the patient's medical history, NYHA functional classification, and clinical

Table 1 Scoring methods for staging the severity of ATTRv-PN [6]

Coutinho Stage	Polyneuropathy Disability Score
0: No symptoms	0: No impairment
1: Unimpaired ambulation; mostly mild sensory, motor, and autonomic neuropathy in the lower limbs	I: Sensory disturbances but preserved walking capability
2: Assistance with ambulation required; mostly moderate impairment progression to the lower limbs, upper limbs, and trunk	II: Impaired walking capability but able to walk without a stick or crutches
3: Wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs	IIIa: Able to walk only with the help of 1 stick or crutch IIIb: Requires the help of 2 sticks or crutches to walk
4: N/A	IV: Confined to a wheelchair or bedridden

ATTRv-PN hereditary transthyretin amyloidosis-polyneuropathy, *N/A* not applicable

laboratory tests. Modified body mass index (mBMI) was determined as BMI in kg/m^2 multiplied by serum albumin in g/l as a measure of nutritional status. Disease severity was evaluated using the Coutinho or polyneuropathy disability (PND) scoring methods (Table 1) and the modified Neuropathy Impairment Score + 7 (mNIS + 7), a modified version of the NIS that was used in the NEURO-TTR trial of inotersen (NCT01737398) [14]. The mNIS + 7 assessment includes the NIS, sensory and motor nerve conduction testing, quantitative sensory testing, and measurement of heart-rate variability with breathing. Two independent mNIS + 7 assessments were performed on sequential days. Neuropathy symptoms were also assessed using a physician-administered Neuropathy Symptoms and Change (NSC) questionnaire, which evaluates the severity of muscle weakness, sensory loss, positive neuropathic sensory symptoms, including pain, and autonomic symptoms [5]. Quality of life was evaluated using the Short Form-36 Physical Component Score (SF-36 PCS) [15], the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) questionnaire [16], and the EuroQol 5-dimension 5-level (EQ-5D-5L) [17]. Patients also underwent a 10-m walk test (10MWT).

Statistical Analysis

Baseline data were analyzed descriptively as means with standard deviation, median and range (minimum/maximum), or numbers and percentages. Characteristics of the NEURO-TTRansform cohort were also analyzed by subgroups based on region (North America, Europe, South America/Australia/Asia), disease onset (early [≤ age 50] or late [> age 50]), previous treatment with TTR stabilizers (yes/no), and TTR sequence variant (V30M or non-V30M).

RESULTS

Demographics and Baseline Disease Characteristics

The NEURO-TTRansform trial enrolled 168 adults with ATTRv-PN (Table 2). Patients were enrolled from sites across 15 countries/territories, including Brazil (n = 40), Portugal (n = 28), Taiwan (n = 23), the USA (n = 23), Argentina (n = 13), Italy (n = 7), Sweden (n = 7), Turkey (n = 7), France (n = 5), Germany (n = 5), Canada (n = 3), Cyprus (n = 3), Spain (n = 2), Australia (n = 1), and New Zealand (n = 1). The mean age of the study group was 52.8 years, with ages ranging from 24 to 82 years. A majority of the patients were White (78.0%) or Asian (14.3%). Approximately two-thirds of the patients (68.5%) had been previously treated with a TTR stabilizer (tafamidis or diflunisal). Most patients (79.2%) had Coutinho stage 1 disease (unimpaired ambulation) and the remaining 20.8% had stage 2 disease (ambulation with

Table 2 Patient demographics and baseline characteristics in the NEURO-TTRansform trial

Parameter	NEURO-TTRansform (*N* = 168)
Age, years	
Mean (SD)	52.8 (14.9)
Median (range)	51.0 (24, 82)
Male, *n* (%)	116 (69.0)
Race, *n* (%)	(*n* = *166*)
White	131 (78.0)
Asian	24 (14.3)
Black or African American	5 (3.0)
Other or multiple	6 (3.6)
Ethnicity, *n* (%)	(*n* = *165*)
Hispanic or Latino	27 (16.1)
Not Hispanic or Latino	138 (82.1)
Region, *n* (%)	
North America[a]	26 (15.5)
Europe[b]	64 (38.1)
South America/Australia/Asia[c]	78 (46.4)
Previous treatment, *n* (%)	
Yes	115 (68.5)
No	53 (31.5)
Previous treatment by type[d], *n* (%)	
Tafamidis	95 (56.5)
Diflunisal	29 (17.3)
Coutinho stage, *n* (%)	
Stage 1	133 (79.2)
Stage 2	35 (20.8)
Disease onset[e], *n* (%)	
Early	89 (53.0)
Late	79 (47.0)
mBMI, $kg/m^2 \times g/l$	(*n* = *160*)
Mean (SD)	1036.2 (237.4)
Median (range)	1017.9 (544.7, 1714.0)
NT-proBNP, pg/ml	(*n* = *167*)
Mean (SD)	429.4 (972.1)
Median (range)	115.0 (8, 6957)
SF-36 PCS score	
Mean (SD)	39.7 (9.3)
Median (range)	39.0 (16.3, 62.2)
PND score, *n* (%)	(*n* = *167*)
I	68 (40.5)
II	69 (41.1)
IIIa	19 (11.3)
IIIb	11 (6.5)
IV	0
TTR sequence variant, *n* (%)	
V30M	101 (60.1)
A97S	23 (13.7)
E89Q	2 (1.2)
L58H	4 (2.4)
F64L	5 (3.0)
S50R	2 (1.2)
S77Y	3 (1.8)
T49A	1 (0.6)
T60A	5 (3.0)
V122I	4 (2.4)
Other	18 (10.7)
Time from diagnosis of ATTRv-PN to enrollment, months	
Mean (SD)	46.6 (57.4)
Median (range)	30.0 (0, 379)
Time from onset of ATTRv-PN symptoms to enrollment, months	(*n* = *167*)

Table 2 continued

Parameter	NEURO-TTRansform (*N* = 168)
Mean (SD)	68.4 (62.7)
Median (range)	52.0 (5, 567)
ATTRv-CM diagnosis[f], *n* (%)	46 (27.4)
Time from ATTRv-CM diagnosis to enrollment, months	(*n* = *46*)
Mean (SD)	18.0 (20.0)
Median (range)	11.0 (1, 89)
Time from onset of ATTRv-CM symptoms to enrollment, months	(*n* = *35*)
Mean (SD)	35.3 (59.8)
Median (range)	18.0 (1, 354)
NYHA functional classification, *n* (%)	
I	122 (72.6)
II	46 (27.4)
mNIS + 7 composite score[g]	
Mean (SD)	79.0 (42.4)
Median (range)	76.2 (7.9, 205.6)
Norfolk QoL-DN total score	(*n* = *161*)
Mean (SD)	43.5 (25.9)
Median (range)	43.0 (1.0, 106.0)
10MWT, m/s	(*n* = *164*)
Comfortable	
Mean (SD)	0.9 (0.3)
Median (range)	0.9 (0.0, 2.9)
Fast	
Mean (SD)	1.2 (0.5)
Median (range)	1.1 (0.0, 3.5)
EQ-5D-5L, visual analog scale	(*n* = *161*)
Mean (SD)	64.2 (18.3)
Median (range)	67.0 (10, 98)
NSC total score	
Mean (SD)	22.8 (12.2)
Median (range)	21.0 (0.0, 60.0)

[a]Canada and the US
[b]Cyprus, France, Germany, Italy, Portugal, Spain, Sweden, and Turkey
[c]Argentina, Australia, Brazil, New Zealand, and Taiwan
[d]Patients could have had both prior tafamidis and diflunisal treatment
[e]Early defined as disease symptoms occurring $\leq$ 50 years of age; late defined as disease symptoms occurring $>$ 50 years of age
[f]The clinical diagnosis was obtained from the case report form
[g]Composite scores on the mNIS + 7 scale range from −22.3 to 346.3, with higher scores indicating poorer function
10MWT 10-m walk test, *ATTRv-CM* hereditary transthyretin amyloidosis-cardiomyopathy, *ATTRv-PN* hereditary transthyretin amyloidosis-polyneuropathy, *ECG* electrocardiogram, *EQ-5D-5L* EuroQol 5-dimension 5-level, *mBMI* modified body mass index (adjusts for serum albumin), *mNIS + 7* modified version of the Neuropathy Impairment Score, *MRI* magnetic resonance imaging, *Norfolk QoL-DN* Norfolk Quality of Life-Diabetic Neuropathy questionnaire, *NR* not reported, *NSC* Neuropathy Symptoms and Change, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *NYHA* New York Heart Association, *PND* Polyneuropathy Disability Score, *SD* standard deviation, *SF-36 PCS* Short Form-36 Physical Component Score, *TTR* transthyretin

assistance). A slightly larger proportion of patients had early-onset (53.0%) compared with late-onset (47.0%) disease. The mean mBMI was 1036 kg/m^2 × g/l, with a range of 545 to 1714 kg/m^2 × g/l. The most prevalent TTR sequence variant overall was V30M (60.1%). The mean time from onset of ATTRv-PN symptoms to study enrollment was 68.4 months, while the mean time from diagnosis of ATTRv-PN to enrollment was 46.6 months.

Table 3 Patient demographics and baseline characteristics by region, disease onset, and prior treatment with TTR stabilizers in the NEURO-TTRansform trial

Parameter	Region			Disease onset[a]		Prior treatment, TTR stabilizer	
	North America (*N* = 26)	Europe (*N* = 64)	South America/ Australia/Asia (*N* = 78)	Early (*N* = 89)	Late (*N* = 79)	Prior Tx (*N* = 115)	Naive (*N* = 53)
Age, years							
Mean (SD)	58.2 (14.1)	50.3 (15.4)	53.0 (14.4)	40.5 (7.7)	66.6 (6.5)	51.3 (14.5)	55.8 (15.3)
Median (range)	65.0 (24, 76)	46.5 (27, 80)	51.0 (25, 82)	41.0 (24, 65)	67.0 (51, 82)	49.0 (25, 80)	58.0 (24, 82)
Male, *n* (%)	13 (50.0)	53 (82.8)	50 (64.1)	62 (69.7)	54 (68.4)	82 (71.3)	34 (64.2)
Race, *n* (%)		(*n* = *62*)			(*n* = *77*)	(*n* = *114*)	(*n* = *52*)
White	22 (84.6)	61 (95.3)	48 (61.5)	76 (85.4)	55 (69.6)	92 (80.0)	39 (73.6)
Asian	0	1 (1.6)	23 (29.5)	7 (7.9)	17 (21.5)	14 (12.2)	10 (18.9)
Black or African American	3 (11.5)	0	2 (2.6)	3 (3.4)	2 (2.5)	4 (3.5)	1 (1.9)
Other or multiple	1 (3.8)	0	5 (6.4)	3 (3.4)	3 (3.8)	4 (3.5)	2 (3.8)
Ethnicity, *n* (%)		(*n* = *61*)			(*n* = *76*)	(*n* = *113*)	(*n* = *52*)
Hispanic or Latino	1 (3.8)	1 (1.6)	25 (32.1)	16 (18.0)	11 (13.9)	17 (14.8)	10 (18.9)
Not Hispanic or Latino	25 (96.2)	60 (93.8)	53 (67.9)	73 (82.0)	65 (82.3)	96 (83.5)	42 (79.2)
Region, *n* (%)							
North America[b]	26 (100.0)	0	0	9 (10.1)	17 (21.5)	11 (9.6)	15 (28.3)
Europe[c]	0	64 (100)	0	40 (44.9)	24 (30.4)	50 (43.5)	14 (26.4)
South America/ Australia/Asia[d]	0	0	78 (100.0)	40 (44.9)	38 (48.1)	54 (47.0)	24 (45.3)
Previous treatment, *n* (%)							
Yes	11 (42.3)[e]	50 (78.1)	54 (69.2)	66 (74.2)	49 (62.0)	115 (100.0)	0
No	15 (57.7)	14 (21.9)	24 (30.8)	23 (25.8)	30 (38.0)	0	53 (100.0)
Previous treatment by type[f], *n* (%)							
Tafamidis	3 (11.5)	49 (76.6)	43 (55.1)	63 (70.8)	32 (40.5)	95 (82.6)	0
Diflunisal	9 (34.6)	5 (7.8)	15 (19.2)	5 (5.6)	24 (30.4)	29 (25.2)	0
Coutinho stage, *n* (%)							
Stage 1	22 (84.6)	55 (85.9)	56 (71.8)	84 (94.4)	49 (62.0)	96 (83.5)	37 (69.8)
Stage 2	4 (15.4)	9 (14.1)	22 (28.2)	5 (5.6)	30 (38.0)	19 (16.5)	16 (30.2)
Disease onset[a], *n* (%)							
Early	9 (34.6)	40 (62.5)	40 (51.3)	89 (100.0)	0	66 (57.4)	23 (43.4)
Late	17 (65.4)	24 (37.5)	38 (48.7)	0	79 (100)	49 (42.6)	30 (56.6)
mBMI, $kg/m^2 \times g/l$		(*n* = *61*)	(*n* = *73*)	(*n* = *85*)	(*n* = *75*)	(*n* = *109*)	(*n* = *51*)
Mean (SD)	1198.1 (244.1)	1003.8 (249.0)	1005.7 (201.9)	998.5 (253.2)	1079.0 (211.6)	1016.2 (234.9)	1078.9 (239.3)

Table 3 continued

Parameter	Region			Disease onset[a]		Prior treatment, TTR stabilizer	
	North America (*N* = 26)	Europe (*N* = 64)	South America/ Australia/Asia (*N* = 78)	Early (*N* = 89)	Late (*N* = 79)	Prior Tx (*N* = 115)	Naive (*N* = 53)
Median (range)	1242.3 (633.8, 1544.4)	935.4 (544.7, 1714.0)	1018.8 (615.7, 1447.7)	948.5 (544.7, 1714.0)	1050.6 (650.4, 1545.8)	980.6 (544.7, 1714.0)	1079.5 (633.8, 1544.4)
NT-proBNP, pg/ml			(*n* = 77)	(*n* = 89)	(*n* = 78)		(*n* = 52)
Mean (SD)	517.4 (1354.8)	497.2 (1053.8)	343.2 (725.1)	233.5 (820.2)	652.8 (1083.4)	355.6 (795.9)	592.4 (1273.1)
Median (range)	102.0 (23, 6957)	107.0 (13, 6287)	118.0 (8, 5455)	64.0 (8, 6957)	242.5 (17, 6287)	90.0 (13, 5455)	177.5 (8, 6957)
SF-36 PCS score							
Mean (SD)	40.2 (11.6)	39.2 (8.9)	39.9 (8.8)	41.4 (9.8)	37.8 (8.3)	40.4 (8.0)	38.1 (11.6)
Median (range)	39.9 (21.8, 62.2)	38.7 (19.3, 55.0)	38.9 (16.3, 60.5)	41.3 (16.3, 62.2)	37.4 (19.8, 53.8)	40.0 (16.3, 57.0)	35.0 (19.3, 62.2)
PND score, *n* (%)			(*n* = 77)		(*n* = 78)		(*n* = 52)
I	15 (57.7)	28 (43.8)	25 (32.1)	42 (47.2)	26 (32.9)	45 (39.1)	23 (43.4)
II	9 (34.6)	27 (42.2)	33 (42.3)	41 (46.1)	28 (35.4)	52 (45.2)	17 (32.1)
IIIa	2 (7.7)	3 (4.7)	14 (17.9)	5 (5.6)	14 (17.7)	12 (10.4)	7 (13.2)
IIIb	0	6 (9.4)	5 (6.4)	1 (1.1)	10 (12.7)	6 (5.2)	5 (9.4)
IV	0	0	0	0	0	0	0
TTR sequence variant, *n* (%)							
V30M	5 (19.2)	50 (78.1)	46 (59.0)	66 (74.2)	35 (44.3)	79 (68.7)	22 (41.5)
A97S	0	0	23 (29.5)	6 (6.7)	17 (21.5)	13 (11.3)	10 (18.9)
E89Q	0	2 (3.1)	0	1 (1.1)	1 (1.3)	2 (1.7)	0
L58H	4 (15.4)	0	0	0	4 (5.1)	3 (2.6)	1 (1.9)
F64L	1 (3.8)	1 (1.6)	3 (3.8)	1 (1.1)	4 (5.1)	2 (1.7)	3 (5.7)
S50R	1 (3.8)	1 (1.6)	0	2 (2.2)	0	1 (0.9)	1 (1.9)
S77Y	1 (3.8)	1 (1.6)	1 (1.3)	0	3 (3.8)	1 (0.9)	2 (3.8)
T49A	0	1 (1.6)	0	1 (1.1)	0	1 (0.9)	0
T60A	5 (19.2)	0	0	0	5 (6.3)	3 (2.6)	2 (3.8)
V122I	3 (11.5)	0	1 (1.3)	2 (2.2)	2 (2.5)	3 (2.6)	1 (1.9)
Other	6 (23.1)	8 (12.5)	4 (5.1)	10 (11.2)	8 (10.1)	7 (6.1)	11 (20.8)
Time from diagnosis of ATTRv-PN to enrollment, months							
Mean (SD)	36.3 (53.0)	63.4 (68.4)	36.2 (44.9)	61.8 (64.3)	29.5 (42.8)	59.8 (60.3)	17.9 (37.0)
Median (range)	16.0 (1, 232)	49.0 (1, 379)	25.0 (0, 250)	45.0 (0, 379)	17.0 (0, 234)	42.0 (2, 379)	5.0 (0, 234)

Table 3 continued

Parameter	Region			Disease onset[a]		Prior treatment, TTR stabilizer	
	North America (*N* = 26)	Europe (*N* = 64)	South America/ Australia/Asia (*N* = 78)	Early (*N* = 89)	Late (*N* = 79)	Prior Tx (*N* = 115)	Naive (*N* = 53)
Time from onset of ATTRv-PN symptoms to enrollment, mean (SD), months			(*n* = 77)		(*n* = 78)		(*n* = 52)
Mean (SD)	77.0 (111.6)	74.7 (45.2)	60.4 (51.6)	72.6 (66.7)	63.7 (57.8)	80.9 (68.8)	40.7 (32.4)
Median (range)	51.5 (8, 567)	70.5 (5, 248)	43.0 (7, 354)	65.0 (5, 567)	46.5 (8, 354)	68.0 (8, 567)	29.5 (5, 141)
ATTRv-CM diagnosis[g], *n* (%)	6 (23.1)	19 (29.7)	21 (26.9)	11 (12.4)	35 (44.3)	30 (26.1)	16 (30.2)
Time from ATTRv-CM diagnosis to enrollment, months	(*n* = 6)	(*n* = 19)	(*n* = 21)	(*n* = 11)	(*n* = 35)	(*n* = 30)	(*n* = 16)
Mean (SD)	12.2 (10.6)	23.7 (27.0)	14.5 (12.9)	18.4 (17.1)	17.9 (21.1)	25.1 (21.5)	4.8 (4.6)
Median (range)	10.0 (1, 30)	7.0 (1, 89)	11.0 (1, 43)	14.0 (1, 46)	11.0 (1, 89)	17.5 (2, 89)	3.5 (1, 17)
Time from onset of ATTRv-CM symptoms to enrollment, months	(*n* = 5)	(*n* = 15)	(*n* = 15)	(*n* = 10)	(*n* = 25)	(*n* = 22)	(*n* = 13)
Mean (SD)	14.6 (11.7)	32.1 (30.0)	45.4 (86.4)	23.4 (25.5)	40.0 (68.8)	46.6 (71.9)	16.1 (20.7)
Median (range)	13.0 (5, 34)	27.0 (1, 87)	19.0 (6, 354)	15.0 (2, 87)	26.0 (1, 354)	30.5 (5, 354)	6.0 (1, 75)
NYHA functional classification, *n* (%)							
I	20 (76.9)	51 (79.7)	51 (65.4)	75 (84.3)	47 (59.5)	86 (74.8)	36 (67.9)
II	6 (23.1)	13 (20.3)	27 (34.6)	14 (15.7)	32 (40.5)	29 (25.2)	17 (32.1)
mNIS + 7 composite score							
Mean (SD)	52.2 (41.5)	78.3 (38.4)	88.5 (42.5)	73.7 (41.6)	84.9 (42.8)	79.7 (41.6)	77.5 (44.5)
Median (range)	35.2 (7.9, 185.0)	70.1 (22.1, 182.4)	91.2 (13.1, 205.6)	67.8 (7.9, 195.5)	84.8 (16.8, 205.6)	75.6 (16.8, 205.6)	84.1 (7.9, 185.0)
Norfolk QoL-DN total score	(*n* = 21)		(*n* = 76)	(*n* = 87)	(*n* = 74)	(*n* = 112)	(*n* = 49)
Mean (SD)	39.3 (26.8)	42.3 (26.2)	45.7 (25.5)	38.8 (25.7)	49.0 (25.1)	42.0 (24.3)	46.8 (29.2)
Median (range)	43.0 (1.0, 87.0)	40.5 (4.0, 104.6)	45.5 (1.0, 106.0)	34.0 (1.0, 106.0)	47.4 (4.0, 102.0)	41.5 (1.0, 106.0)	48.3 (1.0, 102.0)
10MWT, m/s	(*n* = 25)	(*n* = 62)	(*n* = 77)	(*n* = 88)	(*n* = 76)	(*n* = 112)	(*n* = 52)
Comfortable							
Mean (SD)	1.0 (0.3)	0.9 (0.3)	0.9 (0.4)	1.0 (0.3)	0.9 (0.4)	0.9 (0.3)	1.0 (0.3)
Median (range)	1.0 (0.5, 1.6)	0.9 (0.0, 1.6)	0.9 (0.2, 2.9)	1.0 (0.6, 2.9)	0.8 (0.0, 1.6)	0.9 (0.0, 2.9)	1.0 (0.1, 1.6)

Table 3 continued

Parameter	Region			Disease onset[a]		Prior treatment, TTR stabilizer	
	North America (*N* = 26)	Europe (*N* = 64)	South America/ Australia/Asia (*N* = 78)	Early (*N* = 89)	Late (*N* = 79)	Prior Tx (*N* = 115)	Naive (*N* = 53)
Fast							
Mean (SD)	1.3 (0.4)	1.1 (0.6)	1.2 (0.5)	1.2 (0.6)	1.1 (0.5)	1.2 (0.6)	1.2 (0.5)
Median (range)	1.3 (0.5, 1.9)	1.0 (0.0, 3.5)	1.0 (0.3, 3.2)	1.1 (0.5, 3.5)	1.0 (0.0, 2.3)	1.1 (0.0, 3.5)	1.1 (0.1, 2.4)
EQ-5D-5L, visual analog scale		(*n* = *59*)	(*n* = *76*)	(*n* = *86*)	(*n* = *75*)	(*n* = *111*)	(*n* = *50*)
Mean (SD)	68.5 (20.2)	60.1 (19.2)	65.9 (16.4)	63.9 (17.1)	64.5 (19.6)	65.4 (17.2)	61.4 (20.3)
Median (range)	72.5 (30, 98)	60.0 (10, 85)	70.0 (30, 98)	66.5 (25, 98)	67.0 (10, 98)	70.0 (15, 95)	60.0 (10, 98)
NSC total score							
Mean (SD)	15.7 (12.4)	22.2 (11.4)	25.6 (11.8)	22.9 (11.8)	22.7 (12.7)	23.1 (11.4)	22.0 (13.8)
Median (range)	11.3 (1.5, 47.0)	20.3 (3.0, 60.0)	27.3 (0.0, 52.5)	23.5 (0.0, 52.5)	21.0 (2.5, 60.0)	22.5 (1.5, 60.0)	20.0 (0.0, 59.0)

[a]Early defined as disease symptoms occurring ≤ 50 years of age; late defined as disease symptoms occurring > 50 years of age

[b]Canada and the US

[c]Cyprus, France, Germany, Italy, Portugal, Spain, Sweden, and Turkey

[d]Argentina, Australia, Brazil, New Zealand, and Taiwan

[e]Tafamidis and diflunisal are not approved in the US or Canada for use in patients with ATTRv-PN

[f]Patients could have had both prior tafamidis and diflunisal treatment

[g]The clinical diagnosis was obtained from the case report form

10MWT 10-m walk test, *ATTRv-CM* hereditary transthyretin amyloidosis-cardiomyopathy, *ATTRv-PN* hereditary transthyretin amyloidosis-polyneuropathy, *EQ-5D-5L* EuroQol 5-dimension 5-level, *mBMI* modified body mass index (adjusts for serum albumin), *mNIS + 7* modified version of the Neuropathy Impairment Score, *Norfolk QoL-DN* Norfolk Quality of Life-Diabetic Neuropathy questionnaire, *NSC* Neuropathy Symptoms and Change, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *NYHA* New York Heart Association, *PND* Polyneuropathy Disability Score, *SD* standard deviation, *SF-36 PCS* Short Form-36 Physical Component Score, *TTR* transthyretin, *Tx* treatment

Mean 10MWT results were 0.9 m/s (comfortable) and 1.2 m/s (fast).

By geographical region, the greatest number of patients were from South America/Australia/Asia (*n* = 78), followed by Europe (*n* = 64) and then North America (*n* = 26). Across these regions, mean patient ages were 53 years (South America/Australia/Asia), 50 years (Europe), and 58 years (North America); the age ranges were comparable (Table 3). The proportion of male patients was notably higher in the European sites (82.8%) compared with North America (50.0%) and South America/Australia/Asia (64.1%). The North American and European subgroups were predominantly White (84.6% and 95.3%, respectively), while the South America/Australia/Asia subgroup was only about two-thirds White (61.5%) and had the highest proportion of Asian patients (29.5%). The proportion of patients who had previously been treated with TTR stabilizers was highest in Europe (78.1%), followed by South America/Australia/Asia (69.2%) and North America (42.3%). In all regional subgroups, most patients had Coutinho stage 1 disease; South America/Australia/Asia had a higher proportion of patients with Coutinho stage 2 disease (28.2%) compared with North America (15.4%)

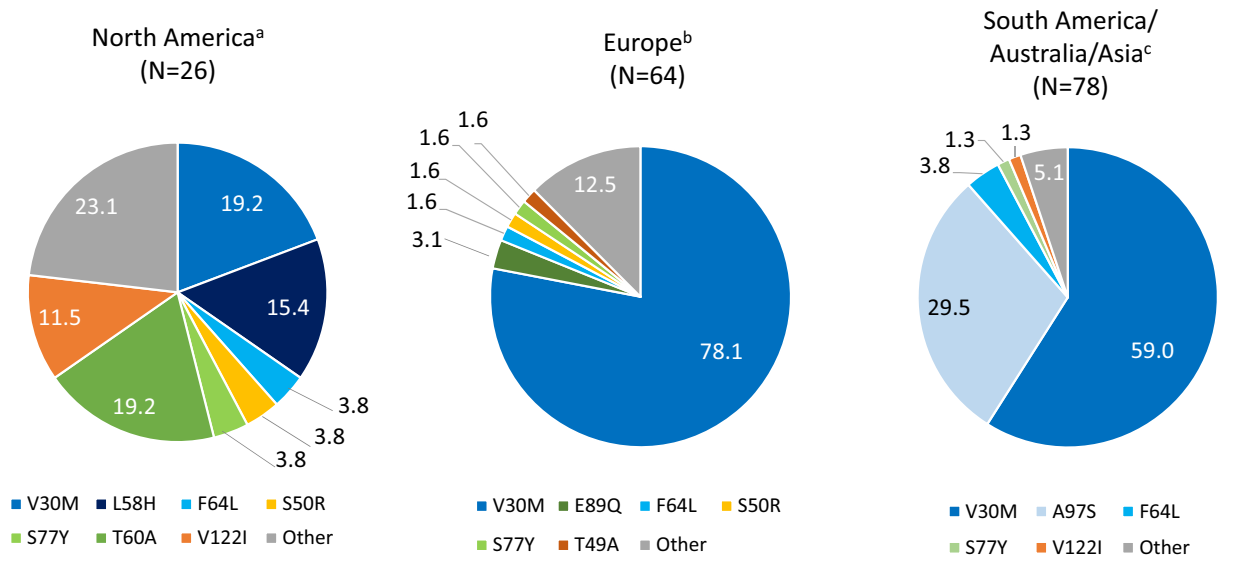

Fig. 1 TTR sequence variant distribution by region in the NEURO-TTRansform trial (percentage of patients). [a]Canada and the US. [b]Cyprus, France, Germany, Italy, Portugal, Spain, Sweden, and Turkey. [c]Argentina, Australia, Brazil, New Zealand, and Taiwan

and Europe (14.1%). Europe had the largest proportion of patients with early-onset disease (62.5%) compared with North America (34.6%) and South America/Australia/Asia (51.3%). Mean mBMI values were similar between Europe (1003.8 kg/m^2 × g/l) and South America/Australia/Asia (1005.7 kg/m^2 × g/l) but slightly higher in North America (1198.1 kg/m^2 × g/l). Geographic subgroups differed greatly regarding specific TTR sequence variant prevalence (Fig. 1). Prevalence of the V30M TTR sequence variant differed between geographic regions with Europe at 78.1%, South America/Australia/Asia at 59.0%, and North America at 19.2%. The most common non-V30M TTR sequence variant was A97S; all were noted in patients from Taiwan. Mean time from ATTRv-PN symptom onset to study enrollment was shortest in patients from South America/Australia/Asia (60.4 months) and comparable in patients from Europe (74.7 months) and North America (77.0 months); however, mean time from ATTRv-PN diagnosis to study enrollment was shorter in patients from South America/Australia/Asia (36.2 months) and North America (36.3 months) than in patients from Europe (63.4 months). The mean time from ATTRv-PN symptom onset to diagnosis varied by region, from 11.2 months in Europe to 23.6 months in South America/Australia/Asia to 40.7 months in North America.

As expected, patients with early versus late disease onset were younger on average (40.5 vs. 66.6 years), and slightly more had a history of previous treatment with tafamidis or diflunisal (74.2% vs. 62.0%). Late-onset cases had a higher proportion of Asian patients (21.5%) relative to early-onset cases (7.9%), yet the proportion of cases represented geographically by South America/Australia/Asia was similar regardless of early vs. late onset (44.9% vs. 48.1%). Nearly all early-onset cases were Coutinho stage 1 (94.4%) compared with 62.0% of late-onset cases. Mean mBMI was lower in the early-onset subgroup than in the late-onset subgroup (998.5 vs. 1079.0 kg/m^2 × g/l). The V30M TTR sequence variant was present in a higher proportion of early vs. late-onset cases (74.2% vs. 44.3%). The mean time from ATTRv-PN diagnosis to study enrollment was twice as long in the early-onset

Table 4 Patient demographics and baseline characteristics by TTR sequence variant in the NEURO-TTRansform trial

Parameter	V30M (*N* = 101)	Non-V30M (*N* = 67)
Age, years		
Mean (SD)	49.8 (15.4)	57.3 (12.9)
Median (range)	44.0 (27, 80)	60.0 (24, 82)
Male, *n* (%)	74 (73.3)	42 (62.7)
Race, *n* (%)	(*n* = *99*)	
White	93 (92.1)	38 (56.7)
Asian	0	24 (35.8)
Black or African American	1 (1.0)	4 (6.0)
Other or multiple	5 (5.0)	1 (1.5)
Ethnicity, *n* (%)	(*n* = *98*)	
Hispanic or Latino	21 (20.8)	6 (9.0)
Not Hispanic or Latino	77 (76.2)	61 (91.0)
Region, *n* (%)		
North America[a]	5 (5.0)	21 (31.3)
Europe[b]	50 (49.5)	14 (20.9)
South America/Australia/Asia[c]	46 (45.5)	32 (47.8)
Previous treatment, *n* (%)		
Yes	79 (78.2)	36 (53.7)
No	22 (21.8)	31 (46.3)
Previous treatment by type[d], *n* (%)		
Tafamidis	78 (77.2)	17 (25.4)
Diflunisal	7 (6.9)	22 (32.8)
Coutinho stage, *n* (%)		
Stage 1	82 (81.2)	51 (76.1)
Stage 2	19 (18.8)	16 (23.9)
Disease onset[e], *n* (%)		
Early	66 (65.3)	23 (34.3)
Late	35 (34.7)	44 (65.7)
mBMI, kg/m^2 × g/l	(*n* = *96*)	(*n* = *64*)
Mean (SD)	1011.8 (236.7)	1073.0 (235.5)
Median (range)	980.5 (544.7, 1714.0)	1046.7 (633.8, 1544.4)
NT-proBNP, pg/ml		(*n* = *66*)

Table 4 continued

Parameter	V30M (*N* = 101)	Non-V30M (*N* = 67)
Mean (SD)	298.9 (796.3)	629.0 (1170.9)
Median (range)	84.0 (8, 6287)	187.5 (10, 6957)
SF-36 PCS score		
Mean (SD)	39.9 (8.2)	39.4 (10.8)
Median (range)	39.7 (16.3, 62.2)	38.6 (19.3, 60.5)
PND score, *n* (%)		(*n* = *66*)
I	35 (34.7)	33 (49.3)
II	49 (48.5)	20 (29.9)
IIIa	10 (9.9)	9 (13.4)
IIIb	7 (6.9)	4 (6.0)
IV	0	0
Time from diagnosis of ATTRv-PN to enrollment, months		
Mean (SD)	59.0 (64.2)	27.9 (38.6)
Median (range)	42.0 (0, 379)	17.0 (0, 234)
Time from onset of ATTRv-PN symptoms to enrollment, months		(*n* = *66*)
Mean (SD)	72.9 (65.6)	61.6 (57.7)
Median (range)	58.0 (7, 567)	48.0 (5, 354)
ATTRv-CM diagnosis[f], *n* (%)	17 (16.8)	29 (43.3)
Time from ATTRv-CM diagnosis to enrollment, months	(*n* = *17*)	(*n* = *29*)
Mean (SD)	23.8 (26.1)	14.6 (14.9)
Median (range)	14.0 (2, 89)	6.0 (1, 46)
Time from onset of ATTRv-CM symptoms to enrollment, months	(*n* = *12*)	(*n* = *23*)
Mean (SD)	28.2 (20.7)	39.0 (72.5)
Median (range)	23.0 (3, 75)	15.0 (1, 354)
NYHA functional classification, *n* (%)		
I	83 (82.2)	39 (58.2)
II	18 (17.8)	28 (41.8)
mNIS + 7 composite score		
Mean (SD)	83.3 (40.3)	72.4 (45.0)
Median (range)	78.2 (7.9, 205.6)	65.5 (13.1, 185.0)
Norfolk QoL-DN total score	(*n* = *100*)	(*n* = *61*)
Mean (SD)	43.9 (24.3)	42.8 (28.5)

Table 4 continued

Parameter	V30M (*N* = 101)	Non-V30M (*N* = 67)
Median (range)	45.0 (1.0, 106.0)	39.0 (1.0, 104.6)
10MWT, m/s	(*n* = *100*)	(*n* = *64*)
Comfortable		
Mean (SD)	0.9 (0.4)	1.0 (0.3)
Median (range)	0.9 (0.0, 2.9)	1.0 (0.2, 1.6)
Fast		
Mean (SD)	1.0 (0.5)	1.4 (0.6)
Median (range)	1.0 (0.0, 2.9)	1.3 (0.3, 3.5)
EQ-5D-5L, visual analog scale	(*n* = *98*)	(*n* = *63*)
Mean (SD)	62.4 (16.3)	67.0 (20.8)
Median (range)	65.0 (15, 90)	70.0 (10, 98)
NSC total score		
Mean (SD)	25.3 (11.0)	19.0 (12.9)
Median (range)	26.0 (1.5, 60.0)	15.5 (0.0, 59.0)

[a]Canada and the US
[b]Cyprus, France, Germany, Italy, Portugal, Spain, Sweden, and Turkey
[c]Argentina, Australia, Brazil, New Zealand, and Taiwan
[d]Patients could have had both prior tafamidis and diflunisal treatment
[e]Early defined as disease symptoms occurring ≤ 50 years of age; late defined as disease symptoms occurring > 50 years of age
[f]The clinical diagnosis was obtained from the case report form
10MWT 10-m walk test, *ATTRv-CM* hereditary transthyretin amyloidosis-cardiomyopathy, *ATTRv-PN* hereditary transthyretin amyloidosis-polyneuropathy, *EQ-5D-5L* EuroQol 5-dimension 5-level, *mBMI* modified body mass index (adjusts for serum albumin), *mNIS + 7* modified version of the Neuropathy Impairment Score, *Norfolk QoL-DN* Norfolk Quality of Life-Diabetic Neuropathy questionnaire, *NSC* Neuropathy Symptoms and Change, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide, *NYHA* New York Heart Association, *PND* Polyneuropathy Disability Score, *SD* standard deviation, *SF-36 PCS* Short Form-36 Physical Component Score, *TTR* transthyretin

compared with the late-onset subgroup (61.8 months vs. 29.5 months), but average times from onset of ATTRv-PN symptoms to study entry showed less variability (72.6 vs. 63.7 months). The prevalence of diagnosed ATTRv-CM was higher among late- compared with early-onset cases (44.3% vs. 12.4%), and mean NT-proBNP values were also higher in the late-onset subgroup (652.8 vs. 233.5 pg/ml). The proportion of patients classified as NYHA functional classification II (mild symptoms and slight limitation during ordinary activity) was also higher in the late-onset subgroup than in the early-onset subgroup (40.5% vs. 15.7%; all other patients were NYHA functional classification I [no symptoms and no limitation in ordinary physical activity]).

Patients with the V30M mutation were slightly younger on average compared with patients with a non-V30M mutation (49.8 vs. 57.3 years); however, the range of patient ages was similar regardless of V30M or non-V30M mutation (Table 4). The V30M subgroup had a slightly higher proportion of male patients

(73.3% vs. 62.7%). Patients with the V30M mutation were almost all White (92.1%), and none were Asian. By contrast, the subgroup with a non-V30M mutation was about one-third Asian (35.8%) and slightly more than one-half White (56.7%). V30M was represented in a similar proportion of patients from Europe (49.5%) and South America/Australia/Asia (45.5%), but rarely in North American patients (5.0%). Coutinho stage distributions were similar at baseline regardless of V30M or non-V30M mutation. ATTRv-CM diagnosed at baseline was notably higher among patients with a non-V30M mutation (43.3% vs. 16.8%), as was the mean NT-proBNP level (629.0 vs. 298.9 pg/ml). The proportion of patients with NYHA functional class II cardiomyopathy was also higher in the non-V30M subgroup compared with the V30M subgroup (41.8% vs. 17.8%). The most prevalent PND score was II in the V30M subgroup (48.5% of patients) and I in the non-V30M subgroup (49.3%). The mean mNIS + 7 score was somewhat higher in the V30M subgroup (83.3 vs. 72.4), as was the NSC total score (25.3 vs. 19.0). The average times from symptom onset and diagnosis of ATTRv-PN to study enrollment were both longer among V30M patients (72.9 and 59.0 months, respectively) compared with non-V30M patients (61.6 and 27.9 months, respectively). Accordingly, the mean time from ATTRv-PN symptom onset to diagnosis was much shorter among V30M patients (13.9 months) than among non-V30M patients (33.3 months). Two-thirds of patients with the V30M mutation had early-onset disease (65.3%), while two-thirds of patients with non-V30M mutations had late-onset disease (65.7%).

Neuropathy Severity Ratings

Severity of neuropathy was assessed at baseline by the PND score, the mNIS + 7, and the NSC total score. Most patients had a PND score of I (40.5%) or II (41.1%) and the rest were III (IIIa or IIIb; 17.9%); no patients had a PND score of IV. The mean mNIS + 7 composite score was 79.0 (scores can range from −22.3 to 346.3, with higher scores representing worse neurologic function [14]). The mean NSC total score was 22.8 (scores can range from 0 to 108 in women or 114 in men, with higher scores representing greater symptom severity [5]).

By geographical region, PND score severity skewed somewhat higher (worse) in the South America/Australia/Asia subgroup relative to Europe and North America; the respective proportions of patients with PND scores of III (IIIa or IIIb) were 24.4%, 14.1%, and 7.7%. Similarly, mean mNIS + 7 composite scores were also the highest (worse) in the South America/Australia/Asia subgroup (88.5) compared with Europe (78.3) and North America (52.2). Patients with late-onset disease were more likely to have a higher (worse) PND score (IIIa or IIIb) compared with those with early-onset disease (30.4% vs. 6.7%), and the late-onset subgroup had a higher mean mNIS + 7 composite score (84.9 vs. 73.7). PND score distributions and mean mNIS + 7 composite scores were generally comparable between prior treatment and treatment-naive subgroups (Table 3).

Quality of Life Characteristics

The QoL burden of ATTRv-PN was assessed using the Norfolk QoL-DN, SF-36 PCS, and EQ-5D-5L instruments. At baseline, the mean Norfolk QoL-DN score was 43.5, which is notably higher (worse) than that reported for healthy volunteers (2.6) [16]. The mean SF-36 PCS score was 39.7, which is lower (worse) than the average score of 50 for the general US population [15]. The mean EQ-5D-5L visual analog scale score at baseline was 64.2 (scale ranging from 0 [worst imaginable health] to 100 [best imaginable health] [18]).

By geographical region, mean Norfolk QoL-DN total scores at baseline were similar across subgroups (North America, 39.3; Europe, 42.3; South America/Australia/Asia, 45.7), as were mean SF-36 PCS scores (40.2, 39.2, and 39.9, respectively) and mean EQ-5D-5L scores (68.5, 60.1, and 65.9, respectively). Mean baseline values for the Norfolk QoL-DN, the SF-36 PCS, and the EQ-5D-5L were also generally similar between early-onset versus late-onset disease

subgroups and between prior treatment and treatment-naive subgroups (Table 3).

Cardiomyopathy-Related Findings

Diagnosis of ATTRv-CM was reported in the medical history of 46 (27.4%) patients and identified an average of 18.0 months prior to study enrollment. Most patients (72.6%) were NYHA class I, and 27.4% were NYHA class II. The proportions of patients with diagnosed ATTRv-CM were similar among the regional subgroups (North America, 23.1%; Europe, 29.7%; South America/Australia/Asia, 26.9%).

DISCUSSION

This summary of baseline patient data from the NEURO-TTRansform trial deepens scientific understanding of the clinical and genetic features of ATTRv-PN. The cohort is diverse regarding demographic features, genetic variant characteristics, and prior treatment for ATTRv-PN and is representative of a global clinical population. Approximately one-quarter of patients were noted to have ATTRv-CM. Baseline evaluations suggested notably impaired QoL among patients with ATTRv-PN in the study relative to reported population norms and healthy volunteers. To provide context for the degree of impairment experienced by patients with ATTRv-PN, prior research has shown the impact on physical function to be more severe than reported for debilitating diseases that are more commonly known, such as Crohn's disease, diabetic retinopathy, or inflammatory bowel disease [10]. The descriptive findings reported here on a large global cohort of individuals with ATTRv-PN from the NEURO-TTRansform phase 3 trial contribute to the scientific understanding of patient characteristics in this rare debilitating disease.

In the NEURO-TTRansform cohort, the mean time from ATTRv-PN symptom onset to diagnosis was 21.5 months (1.8 years). These data highlight the urgency for diagnosis and treatment earlier in the course of this progressive disease before severe multisystem damage has occurred. In a review of literature published from 2005 to 2016 that encompassed more than 500 cases of ATTRv-PN, a 3-year difference was evident between the mean age of symptom onset and mean age of diagnosis [19]. Other data published between 2015 and 2019 indicated median delays between symptom onset and diagnosis ranging from 2.6 to 5 years [20, 21] and mean delays ranging from 4 to 6 years [22]. While the lag between symptom onset and diagnosis has diminished over time, there remains an urgent need for earlier diagnosis and treatment to improve outcomes for patients.

V30M was the most prevalent TTR sequence mutation in patients enrolled in the NEURO-TTRansform study, which is reflective of published literature in this population. In NEURO-TTRansform, the proportion of patients with the V30M variant (60.1%) was somewhat higher than for other phase 3 trials in ATTRv-PN (NEURO-TTR [52%] [23], APOLLO [43%] [24], and HELIOS-A [45%] [25]) and approached the prevalence reported in real-world datasets (e.g., 73% in the THAOS global patient registry) [26]. As expected, the V30M TTR sequence variant was present in both early-onset and late-onset disease. The NEURO-TTRansform population was also reflective of geographic trends in variant distribution, with V30M being more common in European than North American patients [21, 26]. Overall, NEURO-TTRansform includes a V30M cohort that is comparable to other recent phase 3 trials and is representative of real-world populations with ATTRv-PN.

In our study cohort, patients with the V30M mutation had baseline characteristics suggesting greater neuropathy severity and less cardiac involvement than patients with non-V30M mutations, as reported elsewhere [27]. Patients with the V30M mutation were more likely to have early-onset disease, as previously reported [27], with substantially longer time from diagnosis to study enrollment (59 months vs. 28 months for non-V30M). It is not clear if the latter finding is a result of more prevalent and pronounced neuropathy symptoms driving V30M patients to seek medical care earlier in the disease, or a greater awareness of ATTRv-PN in non-North American regions where V30M is more prevalent, or a combination of factors. In

our cohort, all 23 patients from Taiwan had the A97S TTR sequence variant, and this variant was not reported in any other region. This corroborates published data noting a high prevalence of the A97S variant among and generally limited to patients from Taiwan or China and patients of Chinese descent [19, 28–31].

All patients in the NEURO-TTRansform study exhibited some degree of disability due to ATTRv-PN at baseline. Most patients had a PND score of I or II (sensory disturbances, ability to walk with or without a crutch or stick), and the remainder of patients had a PND score of III (walking only with the help of 1–2 crutches or sticks). The NEURO-TTRansform cohort also exhibited substantial impairment in QoL due to ATTRv-PN. Mean Norfolk QoL-DN scores in NEURO-TTRansform were on par with previously reported scores from patients with diabetes with neuropathy, amputation, gangrene, or ulceration [10]. Notably, these disability and QoL impairments were seen despite protocol exclusion of patients with the most severe ATTRv-PN symptoms (e.g., wheelchair-bound or bedridden; severe sensory, motor, and autonomic involvement of all limbs).

Overall, the demographics and clinical characteristics of the NEURO-TTRansform cohort are similar to those of NEURO-TTR [23], with few minor differences. Patients in the NEURO-TTRansform cohort were slightly younger on average than those in the NEURO-TTR cohort (52.8 vs. 59.2 years, respectively) and had less than half the prevalence of diagnosed ATTRv-CM at baseline (27.4% vs. 63%, respectively). The two cohorts also had a different regional distribution of patients, including a lower proportion of patients from North America (15.5% [NEURO-TTRansform] vs. 48% [NEURO-TTR]) and a greater proportion of patients from South America/Australia/Asia (46.4% vs. 17%). The proportion of patients who had been previously treated with TTR stabilizers was slightly higher in the NEURO-TTRansform cohort vs. the NEURO-TTR cohort (68.5% vs. 58%).

A limitation of this manuscript is that study criteria excluded patients with ATTRv-PN who presented with moderate to severe heart failure as measured by the NYHA functional classification (III or higher) and those with previous liver transplantation. Consequently, the baseline characteristics presented here do not include these patient groups, and it is difficult to quantify the proportion of the overall ATTRv-PN population this may have excluded from participation. Based on data from the international THAOS registry (2007–2020), almost half of patients with ATTRv and cardiomyopathy had a NYHA functional classification > II [32]. In other published ATTRv cohorts, the proportion of individuals with a history of liver transplant was 23.1% (THAOS registry, 2007–2011); 20.3% (US, 1970–2013), and 5.7% (Italy, 1991–2020) [21, 26, 33], although liver transplantations have been steadily declining with the recent development of effective pharmacotherapies [34]. Nonetheless, the study cohort included a large proportion of patients with cardiomyopathy diagnosis or symptoms. Another potential limitation is that pooling regions with the smallest number of patients (i.e., South America, Australia, and Asia), which was performed for statistical reasons, could inadvertently introduce bias, as these areas are not geographically, genotypically, or phenotypically linked.

CONCLUSION

In summary, the ongoing, fully enrolled NEURO-TTRansform trial encompasses a diverse population of patients with a wide range of regional, genetic, and disease-severity attributes that are reflective of those in patients with ATTRv-PN who are seen in clinical practice.

ACKNOWLEDGEMENTS

The authors thank the study participants and caregivers.

Funding This study was sponsored by Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA. Medical writing and editorial support were provided by Sandra Westra, PharmD, and Jessica D. Herr, PharmD, of Peloton Advantage, LLC, an OPEN Health company, and funded by Ionis

Pharmaceuticals, Inc., Carlsbad, CA, USA. Ionis Pharmaceuticals, Inc., also provided funding for the journal's Rapid Service Fee.

Author Contributions All authors made substantial contributions to the conceptualization and design of the work and/or the acquisition, analysis, and interpretation of the data. All authors contributed to the drafting and critical review of this manuscript before providing approval for submission of the final version. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures Teresa Coelho: has received financial support to attend scientific meetings from Akcea, Ionis, Alnylam, Pfizer, and Biogen, and receives no personal speaker or consultant honoraria. Márcia Waddington Cruz: has received advisory board and speaker honoraria and financial support for conference attendance from Akcea, Alnylam, Pfizer, and Sobi. Chi-Chao Chao: reports no conflicts of interest. Yeşim Parman: has lectured for Alnylam and Pfizer. Jonas Wixner: has received advisory board and speaker honoraria and financial support for conference attendance from Akcea, Alnylam, and Pfizer. Markus Weiler: has received advisory board and speaker honoraria and financial support for conference attendance from Akcea, Alnylam, Pfizer, and Sobi. Fabio A. Barroso: has received advisory board and speaker honoraria and financial support for conference attendance from Alnylam, Pfizer, and PTC Therapeutics. Noel R. Dasgupta: has received advisory board honoraria from Ionis, Akcea, Alnylam, Pfizer, Eidos, and Intellia, and speaker honoraria from Akcea, Alnylam, and Pfizer. Shiangtung W. Jung: is employed by Ionis. Eugene Schneider: is employed by Ionis. Nicholas J. Viney: is employed by Ionis. P. James B. Dyck: reports no conflicts of interest. Yukio Ando: reports no conflicts of interest. Julian D. Gillmore: has served as an advisor for Alnylam, Ionis, Intellia, Eidos, Pfizer, and ATTRalus. Sami Khella: has served as a consultant to Alnylam, Ionis, Sobi, Pfizer, and Eidos. Morie A. Gertz: has received personal fees from Aptitude, Celgene, Ionis, Akcea, Janssen, Johnson & Johnson, Physicians Education Resource, Prothena, Research to Practice, and Sanofi; health grants and personal fees from Ashfield; financial support for meetings from Juno and Sorrento; fees for serving on a data safety monitoring board from AbbVie; fees for the development of educational materials from i3Health. Laura Obici: has received advisory board and speaker honoraria from Akcea, Alnylam, Pfizer, and Sobi. John L. Berk: has received honoraria for serving on advisory boards for Akcea, Ionis and Eidos, BridgeBio; scientific advisory boards for Corino, and received remotely, Intellia.

Prior Presentation Portions of the data in this manuscript have been presented at: the Peripheral Nerve Society, May 14–17, 2022 in Miami, Florida; the European Academy of Neurology, June 25–28, 2022 in Vienna, Austria; and the International Symposium on Amyloidosis, September 4–8, 2022.

Compliance with Ethics Guidelines The protocol was approved by the institutional review board at the study sites or an independent ethics committee, and trial conduct complied with the Declaration of Helsinki of 1964 and its later amendments, and Good Clinical Practice guidelines. Written informed consent was obtained for all patients prior to enrollment.

Data Availability The datasets generated during and/or analyzed during the current study are not publicly available and the study is ongoing.

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