Patisiran, an Investigational RNAi Therapeutic for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy: Results from the Phase 3 APOLLO Study

D Adams[1], A Gonzalez-Duarte[2], W O'Riordan[3], CC Yang[4], T Yamashita[5], A Kristen[6], I Tournev[7], H Schmidt[8], T Coelho[9], J Berk[10], KP Lin[11], M Sweetser[12], P Gandhi[12], J Chen[12], J Gollob[12], and OB Suhr[13] on behalf of the APOLLO investigators

[1]National Reference Center for FAP (NNERF)/ APHP/ INSERM U 1195/ CHU Bicêtre, Le Kremlin-Bicêtre, France. [2]National Institute of Medical Sciences and Nutrition - Salvador Zubiran (INCMNSZ), Mexico. [3]eStudy Site - La Mesa, United States. [4]National Taiwan University Hospital, Taipei, Taiwan. [5]Kumamoto University Hospital, Kumamoto, Japan. [6]Heidelberg University Hospital, Heidelberg, Germany. [7]University Multiprofile Hospital for Active Treatment, Sofia, Bulgaria. [8]University Hospital of Muenster, Klinik Fur Transplantationsmedizin, Muenster, Germany. [9]. Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal. [10]Amyloid Treatment and Research Program, Boston University, Boston, United States. [11]Neurology Department, Taipei Veterans General Hospital, Taipei, Taiwan. [12]Alnylam Pharmaceuticals, Cambridge, USA; [13]Department of Medicine, Umea University Hospital, Umeå, Sweden.

02 November 2017 | EU ATTR Meeting | Paris

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Hereditary ATTR (hATTR) Amyloidosis

- Rare, inherited, rapidly progressive, debilitating, life-threatening, often fatal disease caused by mutation in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract[1-5]
  - Median survival 2-15 years[1-3]
- Multi-systemic disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms[2,6,7]
  - Disease continuum includes patients who present with predominantly polyneuropathy symptoms (formerly FAP) or cardiomyopathy symptoms (formerly FAC), yet many patients experience a variety of symptoms
  - Clinical manifestations (e.g., disease penetrance and rate of progression) influenced by TTR genotype and geographical region
- Limited treatment options
  - Liver transplant for early-stage disease
  - TTR tetramer stabilizers
    - Tafamidis approved in EU for Stage 1 hATTR amyloidosis[8] and certain other countries outside U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[9]
- Continued high unmet medical need for novel therapeutics

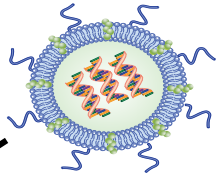
1. Hanna M. Curr Heart Fail Rep. 2014;11(1):50-57; 2. Mohty D et al. Arch Cardiovasc Dis. 2013;106(10):528-540; 3. Adams D et al. Neurology. 2015;85(8):675-682; 4. Damy T et al. J Cardiovasc Transl Res. 2015;8(2):117-127; 5. Hawkins PN et al. Ann Med. 2015;47(8):625-638; 6. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 7. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748 8; Coelho T et al. Neurology. 2012;79:785-92; 9. Berk JL et al. JAMA. 2013;310:2658-67.

Patisiran: Investigational RNAi Therapeutic for hATTR Amyloidosis

Therapeutic Hypothesis

- Lipid nanoparticle formulated RNAi, administered by IV infusion, targeting hepatic production of mutant and wild-type TTR

Patisiran Therapeutic Hypothesis



Patisiran

Production of mutant and wild type TTR

Unstable circulating TTR tetramers ***reduced***

Organ deposition of monomers, amyloid (β-pleated) fibril ***prevented***, ***clearance promoted***

Neuropathy, cardiomyopathy ***stabilization or improvement***

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Patisiran: Investigational RNAi Therapeutic for hATTR Amyloidosis

Clinical Development Program

Phase 1[1]	Phase 2[2]	Phase 2 OLE[3]	Phase 3[4] APOLLO	Global OLE[5]
Completed	Completed	Completed	Completed	Ongoing
Healthy Volunteers	hATTR	hATTR	hATTR	hATTR
Positive results in human healthy volunteers (N=17) • Single dose • 0.01−0.5 mg/kg by IV infusion	**Positive multi-dose results in adult patients with hATTR amyloidosis** (N=29) • Multiple doses • Multiple schedules	**Positive results in adult patients with hATTR amyloidosis with polyneuropathy who participated in the Phase 2 study** (N=27) • 0.3 mg/kg every 3 weeks by IV infusion for up to 2 years	**Adults with hATTR amyloidosis with polyneuropathy** (N=225) • 0.3 mg/kg every 3 weeks by IV infusion for 18 months • Randomized, double-blind, placebo-controlled	**Adults with hATTR amyloidosis with polyneuropathy who participated in the Ph 2 OLE or Ph 3 study** (N=211 enrolled) • 0.3 mg/kg every 3 weeks by IV infusion • Includes some patients with over 3 years treatment

1. Coelho T, et al. N Engl J Med. 2013;369:819-29; 2. Suhr OB, et al. Orphanet J Rare Dis. 2015;10:109;
3. Adams D, et al. Neurology (2017); 88:16 Supplement S27.004 (Clinicaltrials.gov: NCT01961921);4. Clinicaltrials.gov: NCT01960348;
5. Clinicaltrials.gov: NCT02510261

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Patisiran: Investigational RNAi Therapeutic for hATTR Amyloidosis

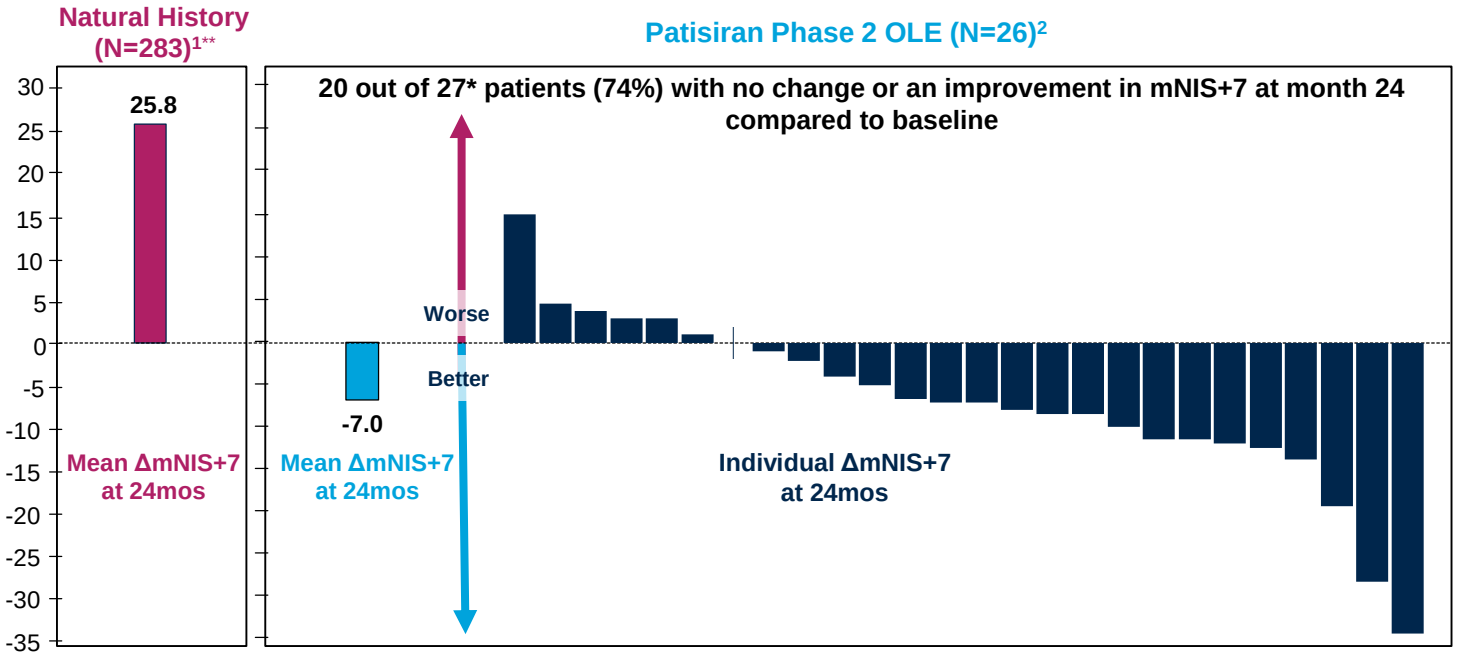
Phase 2 OLE Study Summary

Objectives:

- Primary: Safety and tolerability of long-term dosing with patisiran
- Secondary / Exploratory: Effects on neurologic impairment, QoL, mBMI, disability, mobility, grip strength, autonomic symptoms, nerve fiber density in skin biopsies, cardiac biomarkers and echo (in cardiac subgroup), serum TTR levels

Results:

- Generally well tolerated in patients with hATTR amyloidosis with polyneuropathy out to 25 months with sustained mean serum TTR knockdown of ~80% for over 24 months and improvement in neuropathy impairment score which was consistent with therapeutic hypothesis that patisiran can potentially halt or improve neuropathy progression

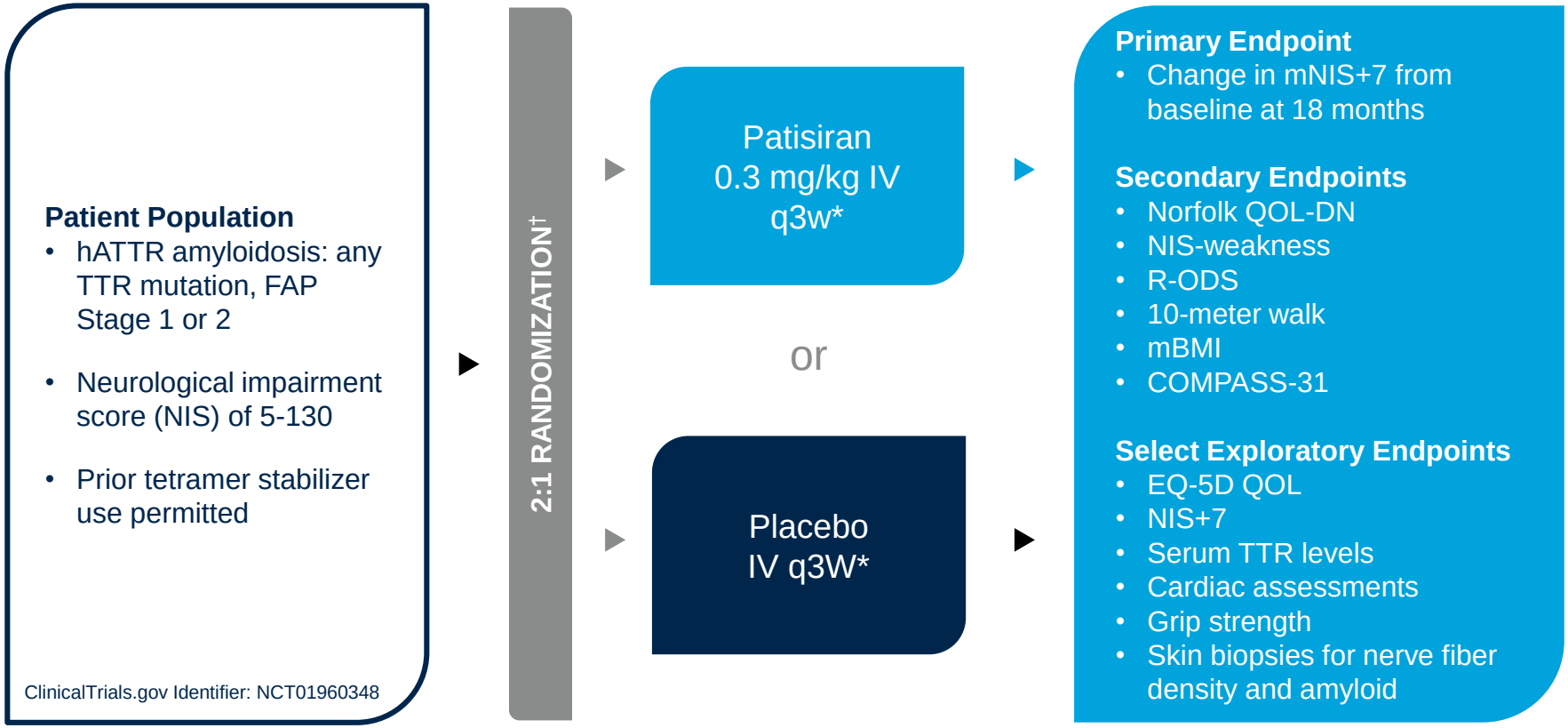


*One patient discontinued prior to the Month 24 assessment and is included in the denominator

[1]Adams D, et al., *Neurology. 85;675-682* (2015); **Predicted progression of median NIS value from Gompertz curve fit

[2]Adams D, et al, AAN 2017

Patisiran Phase 3 APOLLO Study Design



†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous tetramer stabilizer use

*To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine).

Patients who completed study may be eligible for patisiran treatment on Global OLE Study

OLE, open-label extension; ClinicalTrials.gov Identifier: NCT02510261
Adams D, et al. BMC Neurology 2017

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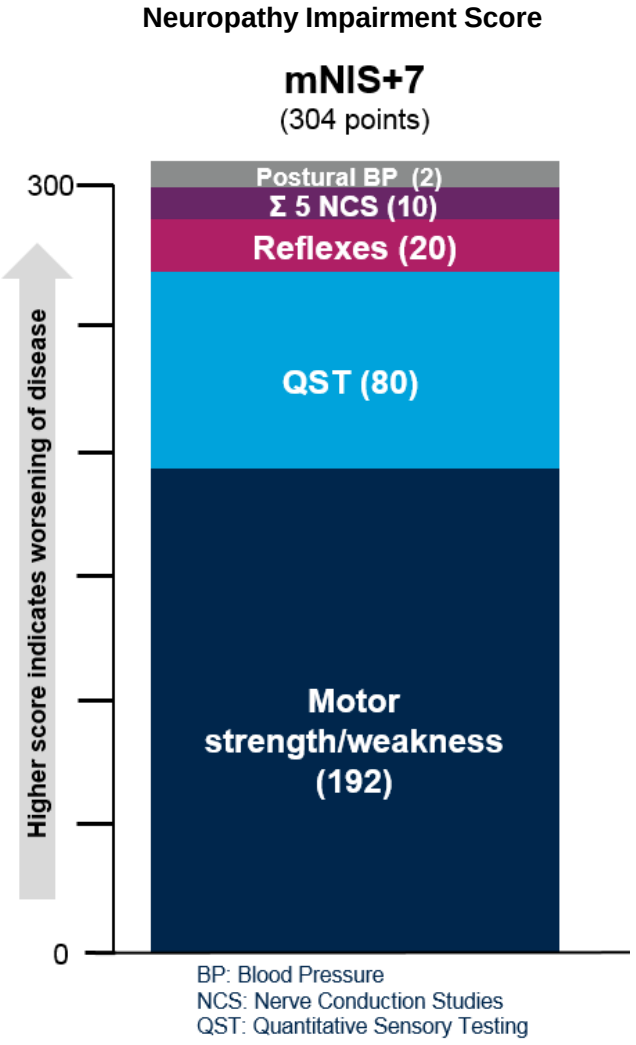
Patisiran Phase 3 APOLLO Study Endpoints

Primary Endpoints

- **mNIS+7:** a composite measure of neurological impairment
  - Higher score indicates worsening of neuropathy

Secondary Endpoints

- **Norfolk QOL-DN:** 35-item QOL questionnaire that is sensitive to small fiber, large fiber, and autonomic nerve function
  - Higher score indicates worsening of QOL
- **NIS-W:** motor function/strength assessment
  - Higher score indicates worsening of strength
- **R-ODS:** 24-item questionnaire used to capture activity and social participation (disability)
  - Lower score indicates worsening disability
- **10-meter walk test (m/sec):** assessment of ambulation that measures gait speed
  - Lower score indicates worsening
- **mBMI (kg/m^2 x albumin [g/L]):** nutritional status
  - Lower score indicates worsening of nutritional status
- **COMPASS-31:** 31-item questionnaire used to evaluate patient reported autonomic neuropathy symptoms
  - Higher score indicates worsening of autonomic neuropathy symptoms



mNIS+7, modified neuropathy impairment scores +7; QOL, quality of life; NIS-W, neuropathy impairment score-weakness; R-ODS, Rasch-built Overall Disability Scale; mBMI, modified body mass index; COMPASS-31, Composite Autonomic Symptom Score questionnaire

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Patisiran Phase 3 APOLLO Study

Primary and Secondary Endpoint Measures

Endpoint	Domain	Range	Improvement
mNIS+7	Neuropathy	0 – 304 points	Negative change
Norfolk QOL-DN	Quality of Life	-4 – 136 points	Negative change
NIS-W	Motor Strength	0 – 192 points	Negative change
R-ODS	Disability	0 – 48 points	Positive change
10-MWT	Ambulation (gait speed)	meters/second (m/sec)	Positive change
mBMI	Nutritional status	kg/m^2 x g/L	Positive change
COMPASS-31	Autonomic Symptoms	0 – 100 points	Negative change

mNIS+7, modified neuropathy impairment scores +7; QOL, quality of life; NIS-W, neuropathy impairment score-weakness; R-ODS, Rasch-built Overall Disability Scale; 10-MWT, 10 meter walk test; mBMI, modified body mass index; COMPASS-31, Composite Autonomic Symptom Score questionnaire

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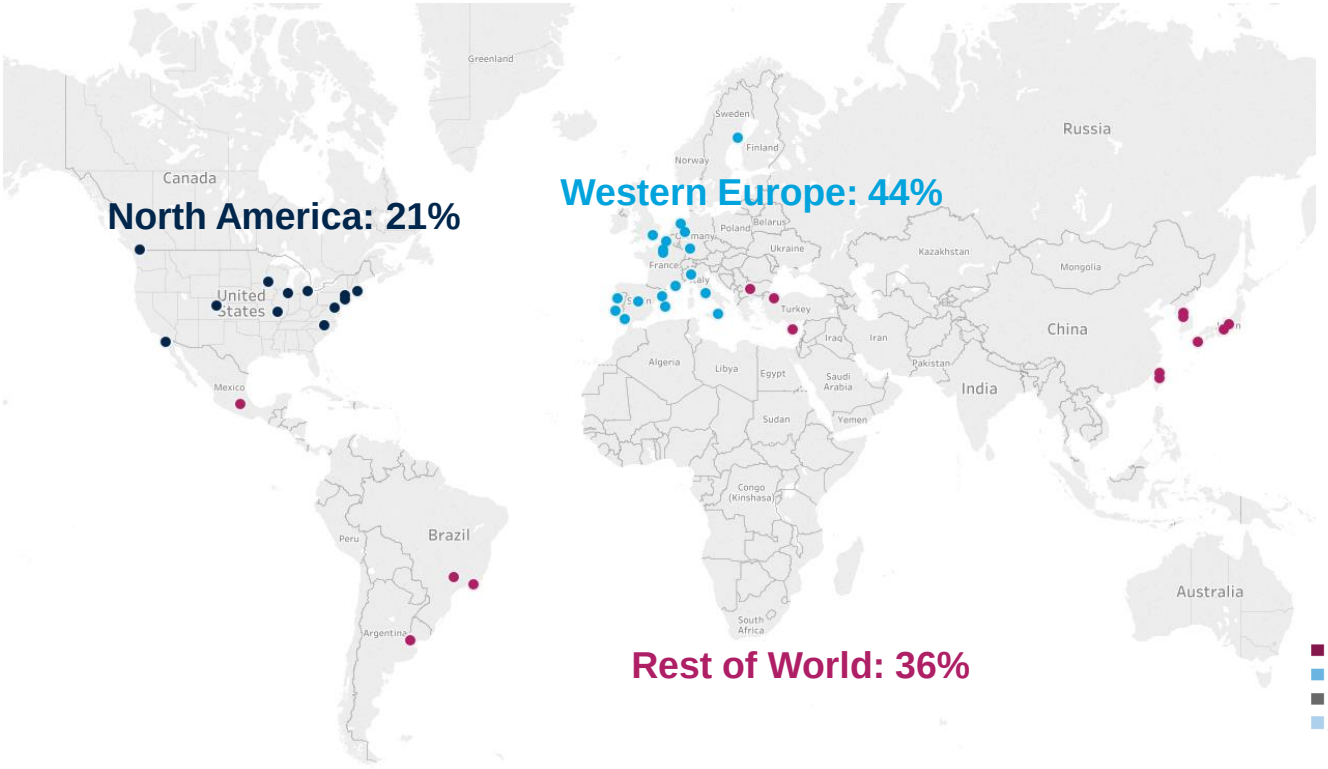
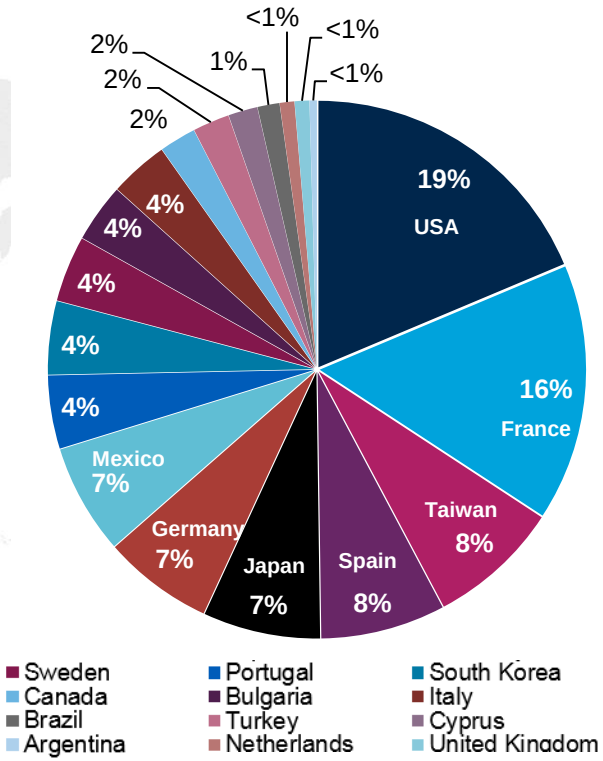
Patisiran Phase 3 APOLLO Study Results

Study Enrollment

225 patients with hATTR amyloidosis with polyneuropathy from 44 sites in 19 countries enrolled between Dec 2013 and Jan 2016





*__North America__: USA, CAN; __Western Europe__: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; __Rest of world__: Asia: JPN, KOR, TWN, *Eastern Europe*: BGR, CYP, TUR; Asia: JPN, KOR, TWN; *Central & South America:* MEX, ARG, BRA

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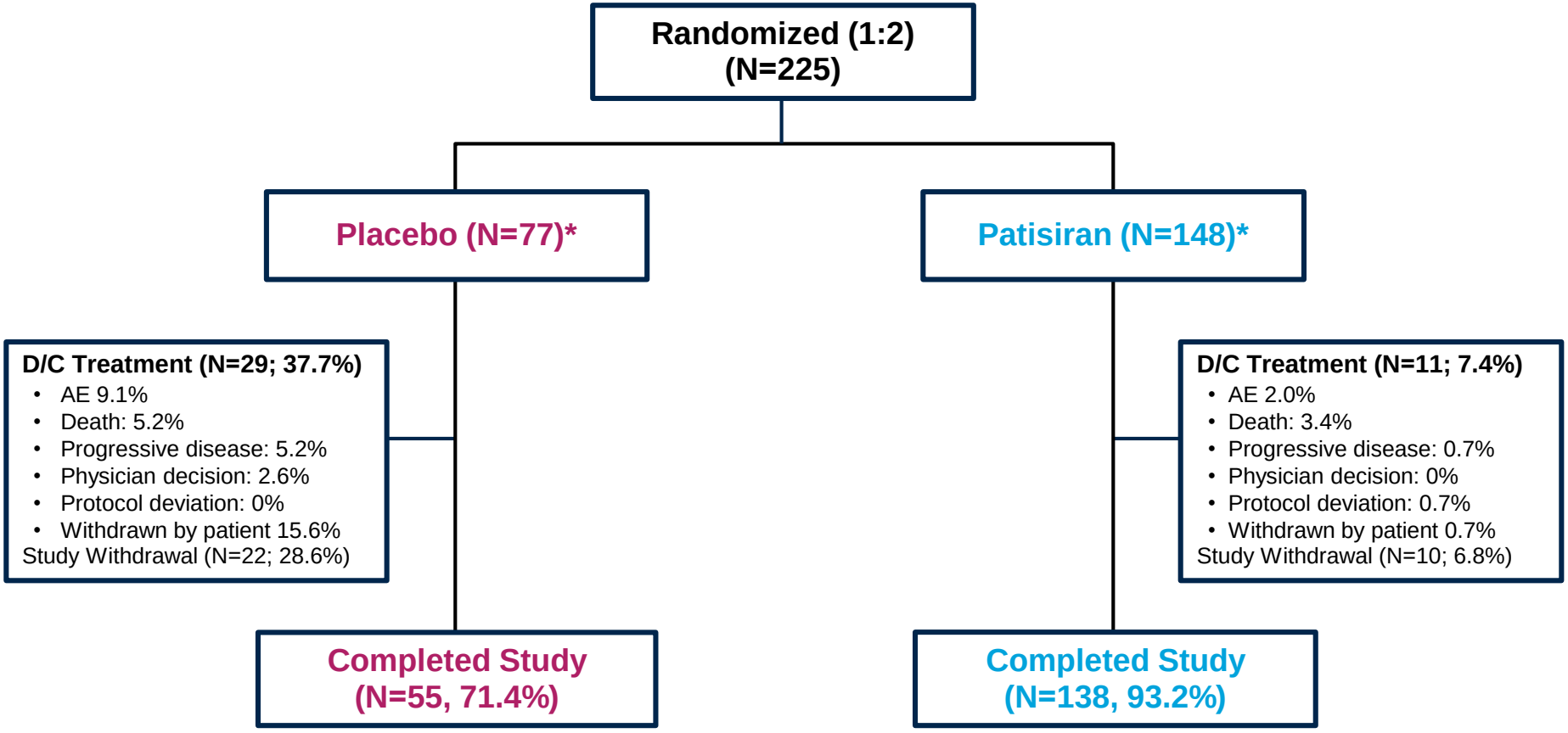
Patisiran Phase 3 APOLLO Study Results

Enrollment and Disposition



*Study populations: modified intent-to-treat (mITT) population: All patients who were randomized and received at least 1 dose of patisiran or placebo (placebo, N=77; patisiran, N=148)

Discontinued (d/c) treatment: patients who permanently stopped treatment prior to the last scheduled dose (Week 78 visit);
Discontinued (d/c) study: patients who stopped the study before any Month 18 (Week 79-80) assessments were performed

Progressive disease: patients who stopped treatment due to rapid disease progression
Rapid disease progression: patients who have ≥24-point increase in mNIS+7 from baseline [based on an average of 2 measurements] and FAP Stage progression relative to baseline at 9 months and had no major protocol deviations

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Patisiran Phase 3 APOLLO Study Results

Baseline Demographics and Disease Characteristics

Characteristic, n (%)	Placebo (N=77)	Patisiran (N=148)
Median Age, years (range)	63 (34, 80)	62 (24, 83)
Gender, males	58 (75.3)	109 (73.6)
Race†		
Asian	**25 (32.5)**	27 (18.2)
Black/African or African American	1 (1.3)	4 (2.7%)
White/Caucasian	50 (64.9)	**113 (76.4)**
Region*		
North America	10 (13.0)	**37 (25.0)**
Western Europe	36 (46.8)	62 (41.9)
Rest of World	31 (40.3)	49 (33.1)
hATTR Diagnosis		
Years since hATTR diagnosis, mean (min, max)	2.60 (0.0, 16.5)	2.39 (0.0, 21.0)
TTR Genotype		
V30M	**40 (51.9)**	56 (37.8)
nonV30M‡	37 (48.1)	**92 (62.2)**
Previous tetramer stabilizer use	41 (53.2)	78 (52.7)

Blue, bolded text indicated ≥10% difference in either group

†Other, patisiran N=1 (0.7%); More than one race, patisiran N=2 (1.4%); missing N=1 each for placebo (1.3%) and patisiran (0.7%)
*__North America__: USA, CAN; __Western Europe__: DEU, ESP, FRA, GBR, ITA, NLD, PRT, SWE; __Rest of world__: *Asia*: JPN, KOR, TWN, *Eastern Europe*: BGR, CYP, TUR; Asia: JPN, KOR, TWN; *Central & South America:* MEX, ARG, BRA
‡Represents 38 different TTR mutations

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Patisiran Phase 3 APOLLO Study Results

Baseline Disease Characteristics, continued

Characteristic, n (%)	Placebo (N=77)	Patisiran (fN=148)
NIS, mean (SEM)		
Mean (min, max)	57.0 (7.0, 125.5)	60.5 (6.0, 141.6)
<50	35 (45.5)	62 (41.9)
≥50 - <100	33 (42.9)	63 (42.6)
≥100	9 (11.7)	23 (15.5)
FAP Stage		
1: unimpaired ambulation	37 (48.1)	67 (45.3)
2: assistance with ambulation required	39 (50.6)	81 (54.7)
3: wheelchair bound or bedridden	1 (1.3)	0
PND Score		
I: preserved walking, sensory disturbances	20 (26.0)	36 (24.3)
II: impaired walking but can walk without stick or crutch	23 (29.9)	43 (29.1)
IIIa: walk with 1 stick or crutch	22 (28.6)	41 (27.7)
IIIb: walk with 2 sticks or crutches	11 (14.3)	28 (18.9)
IV: confined to wheelchair or bedridden	1 (1.3)	0
Cardiac Subpopulation*	36 (46.8)	**90 (60.8)**
NYHA Class I	16 (44.4)	34 (37.8)
NYHA Class II	20 (55.6)	56 (62.2)

Blue, bolded text indicated ≥10% difference in either group

*Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)

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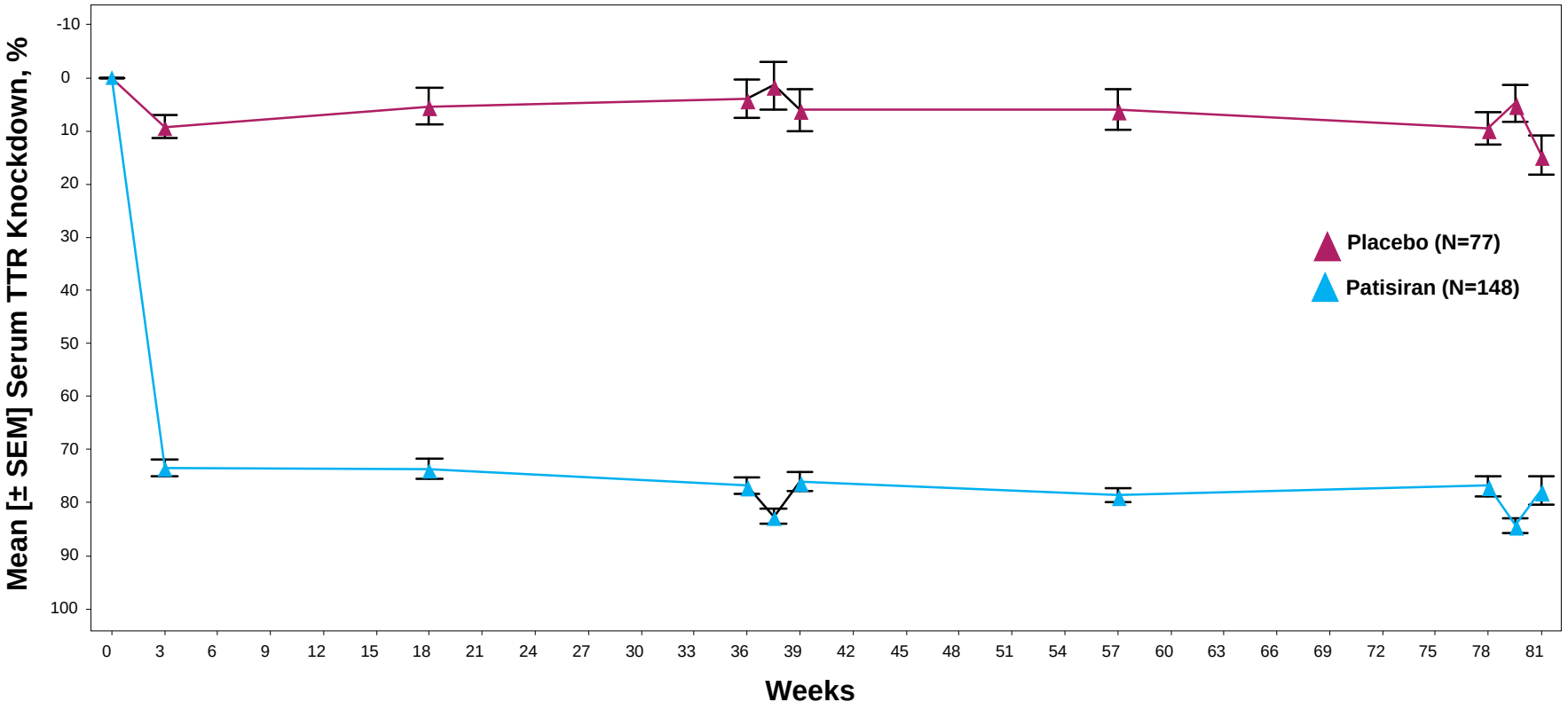
Patisiran Phase 3 APOLLO Study Results

Serum TTR Reduction

87.8% mean max serum TTR reduction from baseline for patisiran over 18 months



TTR Change	Change from baseline at 9 months		Change from baseline at 18 months	
	Placebo (N=77)	Patisiran (N=148)	Placebo (N=77)	Patisiran (N=148)
Mean (SEM) Serum TTR Knockdown	1.5% (4.47)	82.6% (1.36)	4.8% (3.38)	84.3% (1.48)

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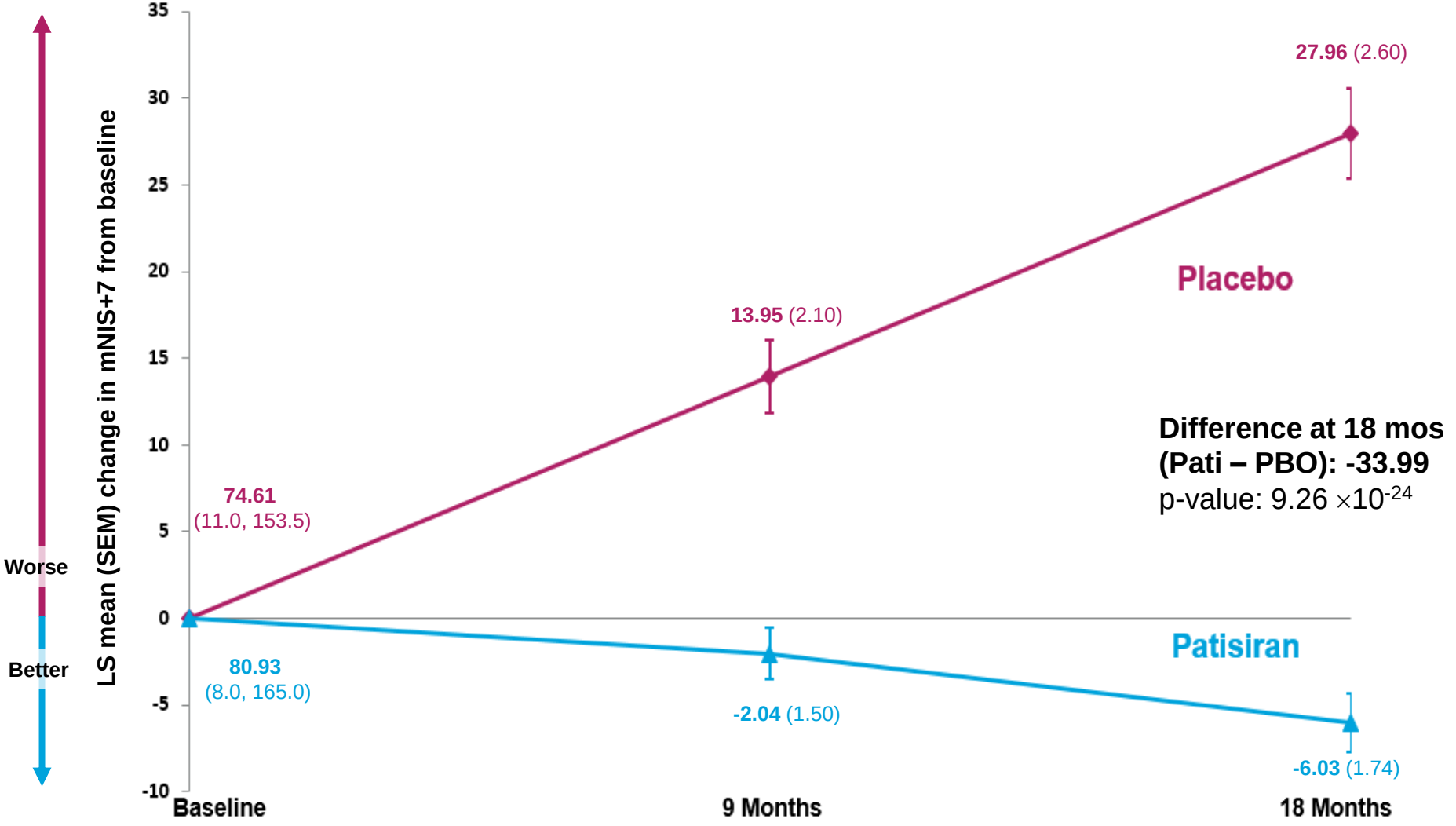
Patisiran Phase 3 APOLLO Study Results

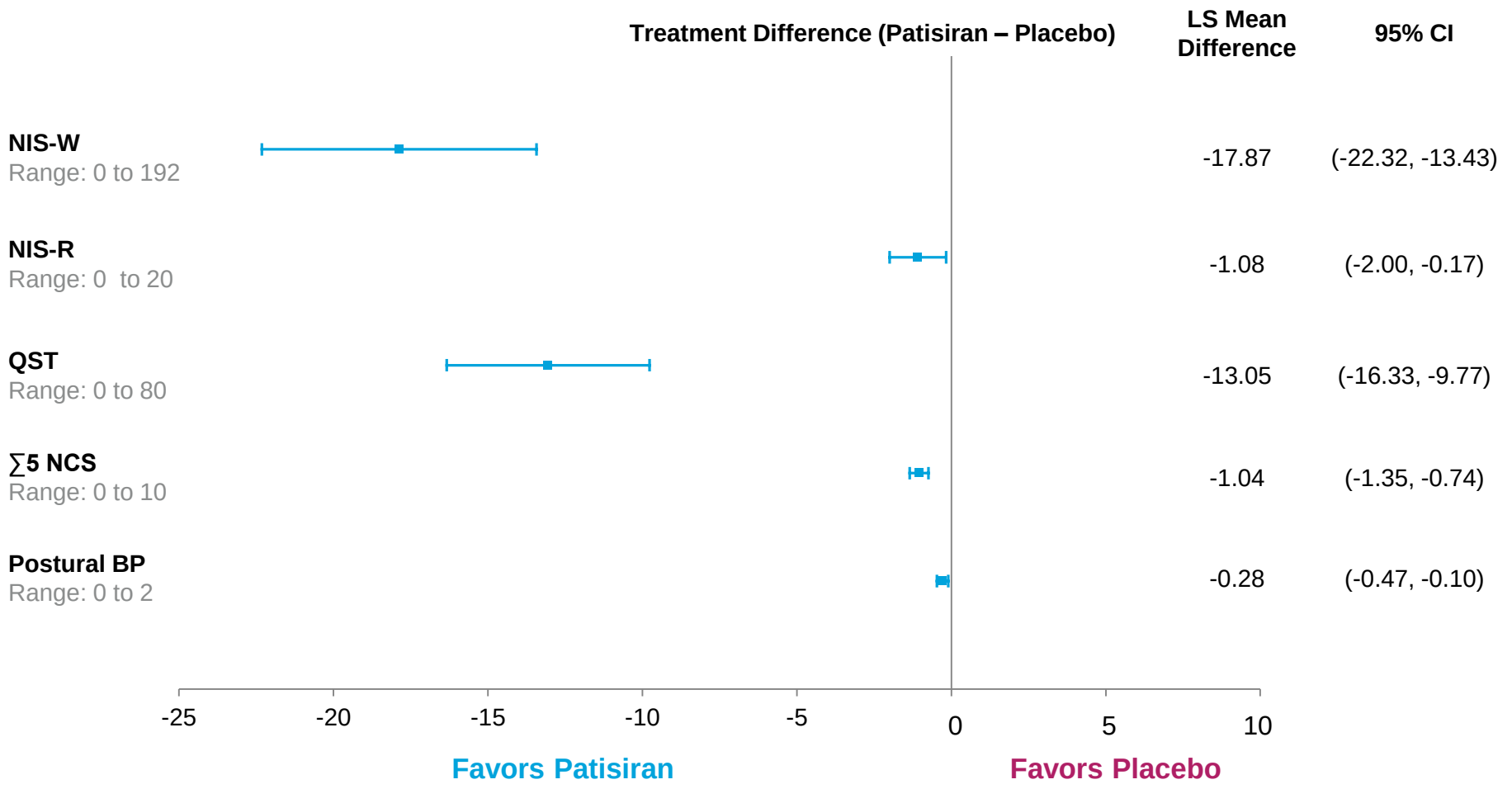
mNIS+7: Change from Baseline



MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
mNIS+7 reference range: 0-304 points

Patisiran Phase 3 APOLLO Study Results

mNIS+7 Subcomponents: Change from Baseline to Month 18



mITT, modified intent to treat; NIS-W, neuropathy impairment score-weakness; NIS-R, neuropathy impairment score-reflexes; QST, Quantitative Sensory Testing; NCS, Nerve Conduction Studies; BP, Blood Pressure

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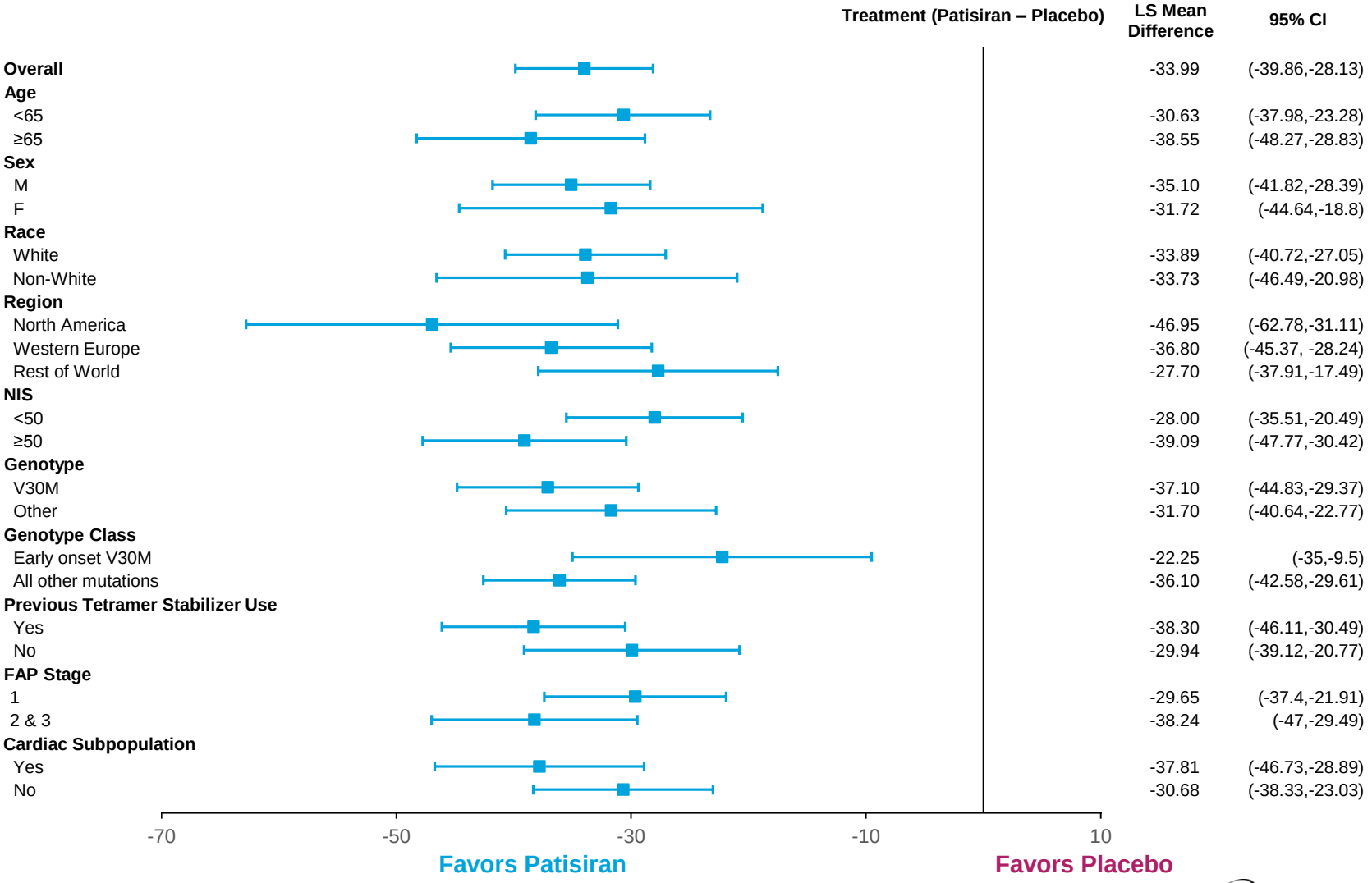
Patisiran Phase 3 APOLLO Study Results

mNIS+7: Change from Baseline to Month 18 in Subgroups



mITT, modified intent to treat

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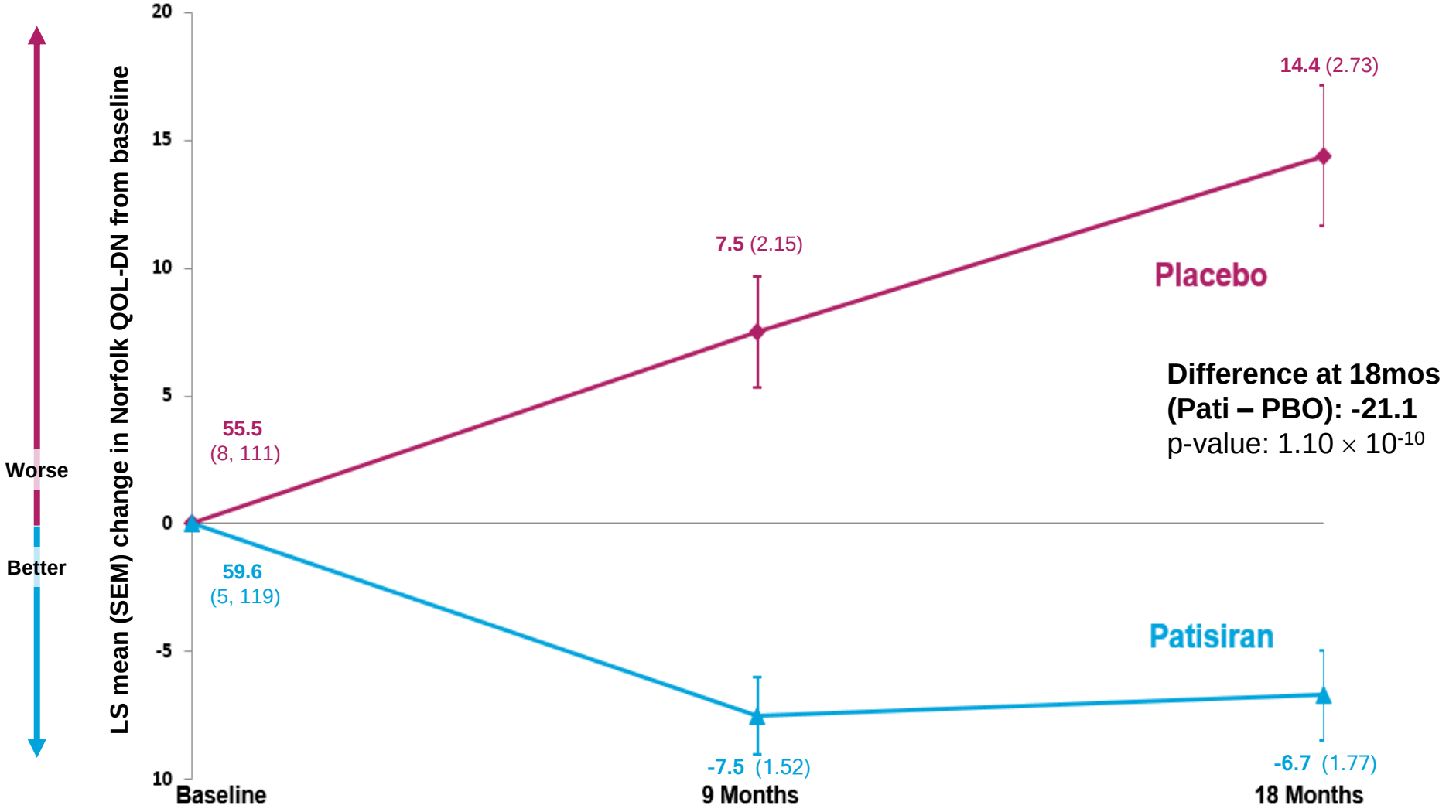
Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline



MMRM, mixed-effects model repeated measures; mITT, modified intent to treat; Pati, patisiran; PBO, placebo; CFB, change from baseline
Norfolk QOL-DN reference range: -4 to 136

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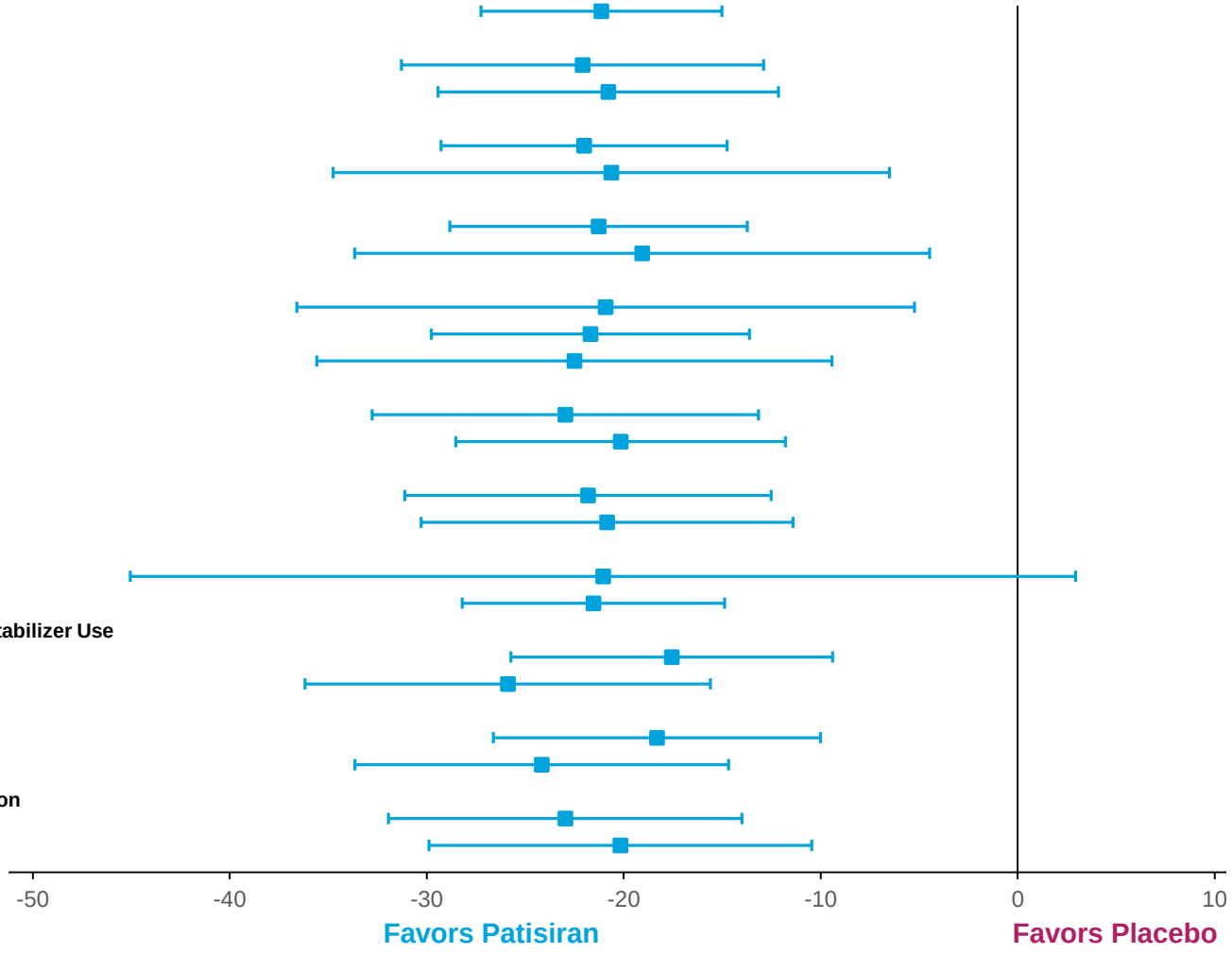
Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline to Month 18 in Subgroups

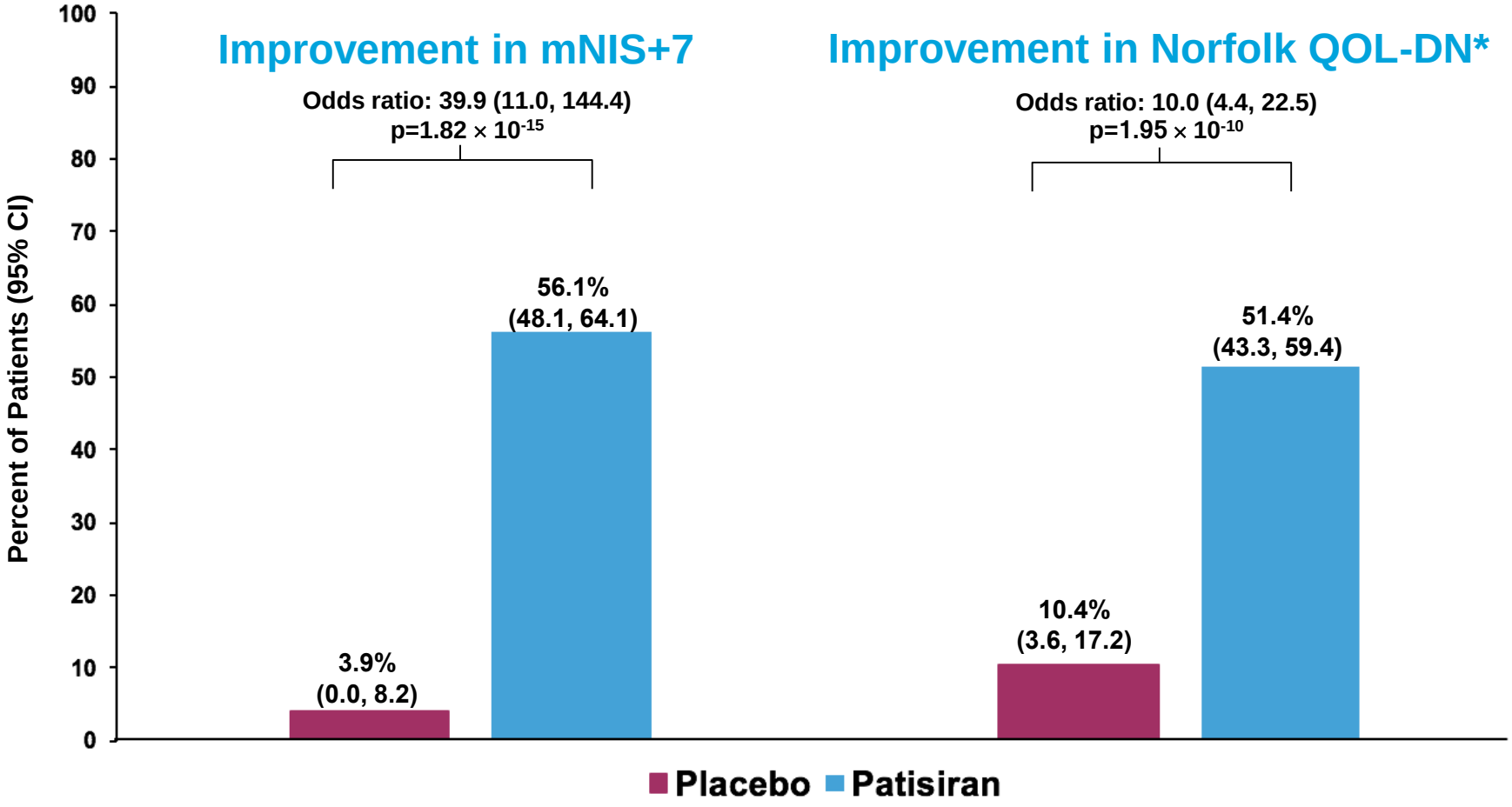


	Treatment Difference (Patisiran – Placebo)	LS Mean Difference	95% CI
Overall		-21.13	(-27.24,-15.01)
Age			
<65		-22.09	(-31.29,-12.89)
≥65		-20.78	(-29.42,-12.13)
Sex			
M		-22.02	(-29.29,-14.76)
F		-20.63	(-34.75,-6.51)
Race			
White		-21.28	(-28.83,-13.74)
Non-White		-19.07	(-33.67,-4.47)
Region			
North America		-20.92	(-36.61,-5.24)
Western Europe		-21.69	(-29.76,-13.62)
Rest of World		-22.50	(-35.58,-9.42)
NIS			
<50		-22.96	(-32.77,-13.15)
≥50		-20.16	(-28.53,-11.8)
Genotype			
V30M		-21.81	(-31.11,-12.5)
Other		-20.84	(-30.27,-11.4)
Genotype Class			
Early onset V30M		-21.05	(-45.05,2.95)
All other mutations		-21.54	(-28.21,-14.88)
Previous Tetramer Stabilizer Use			
Yes		-17.56	(-25.73,-9.39)
No		-25.88	(-36.17,-15.58)
FAP Stage			
1		-18.31	(-26.61,-10.01)
2 & 3		-24.16	(-33.64,-14.67)
Cardiac Subpopulation			
Yes		-22.97	(-31.94,-13.99)
No		-20.17	(-29.88,-10.46)

mITT, modified intent to treat

Patisiran Phase 3 APOLLO Study Results

mNIS+7 and Norfolk QOL-DN: Binary Analysis



Improvement defined as patients with <0 point increase from baseline to 18 months

mITT, modified intent to treat;
*Post-hoc analysis; nominal p-value

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Patisiran Phase 3 APOLLO Study Results

Additional Secondary Endpoints: Change from Baseline (CFB) to 18 Months

All secondary endpoints achieved statistical significance at 18 months

- Nominal statistical significance was achieved as early as month 9 for NIS-W, R-ODS, 10-MWT and mBMI

Secondary endpoint; LS Mean		Placebo (N=77)	Patisiran (N=148)	Treatment Difference (Pati - PBO)	P-Value
NIS-W	Baseline score, mean	29.03	32.69		
	CFB to 18 mos	**17.93**	**0.05**	**-17.87**	**1.40×10^{-13}**
R-ODS	Baseline score, mean	29.8	29.7		
	CFB to 18 mos	**-8.9**	**0.0**	**9.0**	**4.07×10^{-16}**
10-MWT, m/sec	Baseline score, mean	0.79	0.80		
	CFB to 18 mos	**-0.24**	**0.08**	**0.311**	**1.88×10^{-12}**
mBMI, kg/m2 x albumin [g/L]	Baseline score, mean	990	970		
	CFB to 18 mos	**-119.4**	**-3.7**	**115.7**	**8.83×10^{-11}**
COMPASS-31	Baseline score, mean	30.31	30.61		
	CFB to 18 mos	**2.24**	**-5.29**	**-7.53**	**0.0008**

Pati, patisiran; PBO, placebo; NIS-W, neuropathy impairment score-weakness; CFB, change from baseline; R-ODS, Rasch-built Overall Disability Scale; 10-MWT, 10 meter walk test; mBMI, modified body mass index; COMPASS-31, Composite Autonomic Symptom Score questionnaire

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Patisiran Phase 3 APOLLO Study

Exploratory Cardiac Endpoints

Exploratory Endpoint	Measures	Normal Value	Improvement
Cardiac biomarkers			
NT-proBNP, ng/L	Cardiac stress	<125*	Reduction
Troponin-I, mg/L	Myocardial injury	≤ 0.1	Reduction
Echocardiogram			
LV wall thickness, cm	Cardiac amyloid burden	< 1.2	Reduction
LV Mass, g	Cardiac amyloid burden	155 (M), 103 (F)	Reduction
Longitudinal Strain, %	Systolic function	-15.9 to -21.1	Reduction
LV ejection fraction, %	Systolic function	>50	Increase
Functional Status			
10-MWT gait speed, m/sec	ambulation	1.1 – 1.3‡	Increase

M, Male; F, female; LV, left ventricular, 10-MWT, 10 meter walk test
*Age up to 75 years; ‡Age 10-79

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Patisiran Phase 3 APOLLO Study Results

Exploratory Analysis: Cardiac Subpopulation*

Patients within cardiac subpopulation had substantial cardiac involvement

Exploratory endpoint		Placebo (N=36)	Patisiran (N=90)	Treatment Difference (Pati - PBO)	Nominal p-value
Cardiac biomarkers					
NT-proBNP, ng/L	Baseline, median	845.7	756.4		
	CFB to 18 mos, median‡	**320.4**	**-49.9**	**-370.2**	**7.74×10^{-8}**
Troponin-I, mg/L	Baseline, mean	0.11	0.12		
	CFB to 18 mos, LS mean	**0.0**	**0.004**	**0.004**	**0.87**
Echocardiogram					
LV wall thickness, cm	Baseline, mean	1.64	1.68		
	CFB to 18 mos, LS mean	**-0.007**	**-0.100**	**-0.093**	**0.0173**
LV Mass, g	Baseline, mean	264.52	275.48		
	CFB to 18 mos, LS mean	**0.63**	**-15.12**	**-15.75**	**0.15**
Longitudinal Strain, %	Baseline, mean	-15.66	-15.13		
	CFB to 18 mos, LS mean	**1.46**	**0.08**	**-1.37**	**0.0154**
LV ejection fraction, %	Baseline, mean	62.2	60.0		
	CFB to 18 mos; LS mean	**0.57**	**1.00**	**0.43**	**0.78**
Functional Status					
10-MWT gait speed, m/sec	Baseline, mean	0.73	0.78		
	CFB to 18 mos; LS mean	-0.35	0.01	**0.35**	**7.42×10^{-9}**

*Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)
Pati, patisiran; PBO, placebo; CFB, change from baseline
‡P-value based on changes in log-transformed data

APOLLO

Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability

Type of Adverse Event, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Adverse event (AE)	75 (97.4)	143 (96.6)
Severe AE	28 (36.4)	42 (28.4)
Serious adverse event (SAE)	31 (40.3)	54 (36.5)
AE leading to treatment discontinuation	11 (14.3)	7 (4.7)
AE leading to study withdrawal	9 (11.7)	7 (4.7)
Death	6 (7.8)	7 (4.7)

Overall, 13 deaths in APOLLO study; no deaths considered related to study drug

- Similar frequency of deaths in patisiran and placebo treatment groups
- Causes of death (e.g., cardiovascular, infection) consistent with natural history

APOLLO

APOLLO - Patisiran Phase 3 Study

Serious Adverse Events ≥ 2% in any Treatment Group

Preferred Term; number of patients (%)	Placebo (N=77)	Patisiran (N=148)
At least 1 SAE	31 (40.3)	54 (36.5)
Diarrhea	1 (1.3)	**8 (5.4)**
Cardiac failure	2 (2.6)	3 (2.0)
Cardiac failure congestive	2 (2.6)	3 (2.0)
Orthostatic hypotension	1 (1.3)	3 (2.0)
Pneumonia	3 (3.9)	3 (2.0)
Atrioventricular block complete	0	3 (2.0)
Acute kidney injury	**4 (5.2)**	1 (0.7)
Dehydration	**3 (3.9)**	1 (0.7)
Vomiting	**3 (3.9)**	1 (0.7)
Urinary tract infection	**4 (5.2)**	0
Constipation	2 (2.6)	0
Hereditary neuropathic amyloidosis	2 (2.6)	0
Hyponatremia	2 (2.6)	0
Pneumonia aspiration	2 (2.6)	0

Blue, bolded text indicated ≥3 percentage point difference in individual preferred terms in either group

No increases in observed frequency of events for patisiran compared to placebo group by system organ class:

- Cardiac disorders: 13.0% placebo, 13.5% patisiran
- Gastrointestinal disorders: 7.8% placebo, 8.8% patisiran
- Hepatobiliary disorders: 1.3% placebo, 0.7% patisiran
- Infections and infestations: 11.7% placebo, 5.4% patisiran
- Renal and urinary disorders: 6.5% placebo, 0.7% patisiran

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Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability: Common Adverse Events

Majority of AEs were mild or moderate in severity

- Peripheral edema
  - Did not result in any treatment discontinuations
  - Decreased over time
- Infusion-related reactions (IRRs)
  - Majority mild in severity
  - No severe, life-threatening or serious IRRs
  - Decreased over time
  - Led to treatment discontinuation in 1 patient

No safety signals regarding cataracts, hyperglycemia, infection, or osteopenia/ osteoporosis

No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

Adverse Events Occurring in ≥ 10% in Either Group

Preferred AE Term, number of patients (%)	Placebo (N=77)	Patisiran (N=148)
Diarrhea	29 (37.7)	55 (37.2)
Edema, peripheral	17 (22.1)	**44 (29.7)**
Infusion related reaction (IRR)	7 (9.1)	**28 (18.9)**
Fall	**22 (28.6)**	25 (16.9)
Constipation	13 (16.9)	22 (14.9)
Nausea	**16 (20.8)**	22 (14.9)
Dizziness	11 (14.3)	19 (12.8)
Urinary tract infection	**14 (18.2)**	19 (12.8)
Fatigue	8 (10.4)	18 (12.2)
Headache	9 (11.7)	16 (10.8)
Cough	9 (11.7)	15 (10.1)
Insomnia	7 (9.1)	15 (10.1)
Nasopharyngitis	6 (7.8)	15 (10.1)
Vomiting	8 (10.4)	15 (10.1)
Asthenia	9 (11.7)	14 (9.5)
Pain in Extremity	8 (10.4)	10 (6.8)
Muscular Weakness	**11 (14.3)**	5 (3.4)
Anemia	**8 (10.4)**	3 (2.0)
Syncope	**8 (10.4)**	3 (2.0)

Blue, bolded text: Indicates ≥5 percentage point difference in either group

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Patisiran Phase 3 APOLLO Study Results

Safety and Tolerability: Cardiac Subpopulation*

Type of Adverse Event, number of patients (%)	Placebo (N=36)	Patisiran (N=90)
Any adverse event	35 (97.2)	86 (95.6)
Cardiac Disorders SOC	13 (36.1)	29 (32.2)
Any serious adverse event	**18 (50.0)**	31 (34.4)
Cardiac Disorders SOC	4 (11.1)	13 (14.4)
Cardiac Arrhythmias (HGLT)	**11 (30.6)**	17 (18.9)
Torsades de Pointes (SMQ)‡	5 (13.9)	7 (7.8)
Deaths	4 (11.1)	5 (5.6)

Blue, bolded text indicated ≥10 percentage point difference in either group

*Pre-specified cardiac subpopulation: patients with evidence of pre-existing cardiac amyloid involvement at baseline without confounding medical conditions (i.e., patients with baseline left ventricular [LV] wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)
SOC, System Organ Class; HGLT, high-level group term; SMQ, standardized MedDRA queries
‡Torsades de Pointes SMQ is a search for reported events that may be associated with Torsades. It does not mean that these are confirmed events of Torsades de pointes; no cases of Torsades de pointes have been reported

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Patisiran Phase 3 APOLLO Study Summary

hATTR amyloidosis is a multi-systemic, progressive, debilitating, life-threatening, often fatal disease disease with high morbidity and mortality and limited therapeutic options

Patisiran treatment resulted in significant improvement in polyneuropathy relative to placebo

- Benefits seen in motor, sensory and autonomic neuropathy
- Positive effects observed across wide range of disease severity and TTR genotypes, including patients with cardiac involvement

Significant reduction in disease symptoms and disability, improvement in quality of life, nutritional status, strength, and ambulation seen with patisiran relative to placebo

Favorable and significant changes in exploratory cardiac measures in patisiran treated patients within cardiac subpopulation

- Clinically significant improvement in NT-proBNP, longitudinal strain and LV wall thickness and associated improvement in ambulation (10-MWT gait speed) relative to placebo

Patisiran was generally well tolerated in patients with hATTR amyloidosis for 18 months

- Similar frequency of deaths in patisiran and placebo groups; none were considered drug-related
- Key patisiran safety findings include mild to moderate peripheral edema and IRRs with only one treatment discontinuation due to these events
- No safety signals with regard to thrombocytopenia, hepatic or renal dysfunction
- Safety in cardiac subpopulation comparable to overall study population

99% of eligible APOLLO patients enrolled into Global OLE study

APOLLO

Acknowledgments

Thank you to the patients and their families, investigators, study staff and collaborators for their participation in the Phase 3 APOLLO study

Study Investigators

- Adams, David: CHU Bicetre , France
- Ajroud-Driss, Senda: Northwestern University, USA
- Attarian, Shahram: Hôpital de La Timone, France
- Barroso, Fabio: Instituto FLENI Montaneses, Argentina
- Berk, John: Boston University, USA
- Brannagan, Thomas: Columbia University Medical Center, USA
- Buades Reines, Juan: Hospital Son Llatzer, Spain
- Campistol, Joseph: Hospital Clinic, ICNU, Spain
- Coelho, Teresa: Hospital de Santo António, Portugal
- Conceicao, Isabel: Hospital de Santa Maria, Portugal
- Marques Junior, Wilson: Hospital das Clinicas da USP de Ribeirao, Brazil
- Dispenzieri, Angela: Mayo Clinic, USA
- Galan Davila, Lucia: Hospital Clinic San Carlos, Spain
- Gonzalez-Duarte, Alejandra: National Institute of Med Sciences, Mexico
- Gorevic, Peter: Mount Sinai Medical Center, USA
- Hazenberg, Bouke: UMC, Netherlands
- Ito, Mizuki: Nagoya University Hospital, Japan
- Kim, Byoung-Joon: Samsung Medical Center, South Korea
- Kristen, Arnt: Heidelberg University Hospital, Germany
- Kyriakides, Theodoros: CING, Cyprus
- Lin, Kon-Ping: Taipei Veterans General Hospital, Taiwan
- Lopate, Glenn: Washington University School of Medicine Center, USA
- Mezei, Michelle: Vancouver General Hospital, Canada
- Munoz Beamud, Francisco: Juan Ramon Jimenez Hospital, Spain
- Obici, Laura: Fondazione IRCCS Policlinico San Matte, Italy
- Oh, Jeeyoung: Konkuk University Hospital, South Korea
- O'Riordan, William: eStudy Site, USA
- Parman, Yesim: Istanbul University, Turkey
- Plante-Bordeneuve, Violaine: CHU Henri, France
- Polydefkis, Michael: Johns Hopkins Bayview Medical Center, USA
- Quan, Dianna: University of Colorado - Aurora, USA
- Sabatelli, Mario: Universita Cattolica del Sacro Cuore Institute of Neurology, Italy
- Schmidt, Hartmut: University Hospital of Muenster, Germany
- Sekijima, Yoshiki: Shinshu University Hospital, Japan
- Suhr, Ole: Umea University Hospital, Sweden
- Tard, Celine: CHRU de Lille, France
- Taubel, Jorg: St George's University of London, UK
- Tournev, Ivaylo: UMHAT Aleksandrovska, Bulgaria
- Tuchman, Sascha: Duke University Medical Center, USA
- Vita, Giuseppe: Policlinico Universitario, Italy
- Waddington-Cruz, Marcia: Hospital Universitario Clementino Fraga Filho, Brazil
- Yamashita, Taro: Kumamoto Univ. Hospital, Japan
- Yang, Chih-Chao: National Taiwan University Hospital, Taiwan
- Zonder, Jeffrey: Karmanos Cancer Institute, USA

Study Collaborators

- Peter Dyck: Mayo Clinic, Rochester, MN USA

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Leo
Living with hATTR Amyloidosis

THANK YOU!

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