

# Impact of Patisiran on Norfolk Quality of Life Questionnaire Diabetic Neuropathy (QOL-DN) in Patients with Hereditary Transthyretin-Mediated Amyloidosis: Results from the Phase 3 APOLLO Study

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# Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

## Disease Overview and Introduction to Patisiran, an Investigational RNAi Therapeutic

- hATTR Amyloidosis

- Rare, inherited, rapidly progressive, debilitating, life-threatening disease caused by mutations in transthyretin (TTR) gene resulting in misfolded TTR protein accumulating as amyloid fibrils in nerves, heart, and gastrointestinal tract<sup>1-5</sup>
- Median survival 4.7 years following diagnosis<sup>6</sup>; reduced survival (3.4 years) for patients presenting with cardiomyopathy<sup>6-8</sup>

- Multisystem disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms<sup>2,9,10</sup>

- 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) are influenced by TTR genotype and geographical region

- Limited treatment options

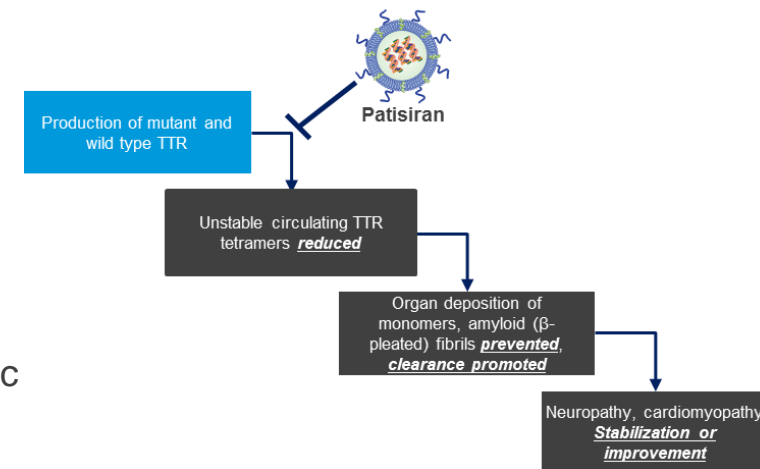
- Liver transplant for early-stage disease and TTR tetramer stabilizers
  - Tafamidis approved in EU for Stage 1 hATTR amyloidosis<sup>11</sup> and certain other countries outside U.S.
  - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study<sup>12</sup>

- Continued high unmet medical need for novel therapeutics

- Patisiran, an Investigational RNAi Therapeutic

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

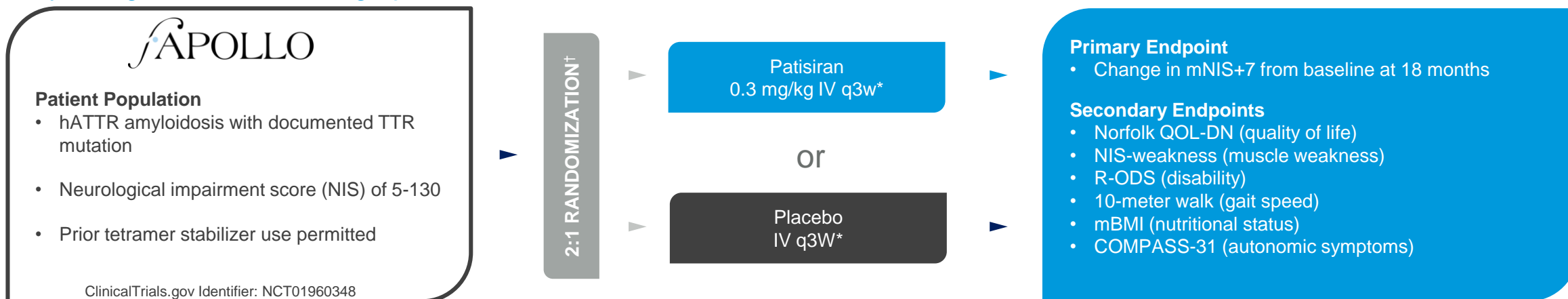
### Patisiran Therapeutic Hypothesis



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. Swiecicki PL et al. Amyloid 2015;22(2):123-31; 7. Sattianayagam AJ et al. Eur Heart J 2012;33:1120-7; 8. Gertz MA et al. Mayo Clin Proc 1992;67(5):428-40; 9. Conceição I et al. J Peripher Nerv Syst. 2016;21(1):5-9; 10. Shin SC et al. Mt Sinai J Med. 2012;79(6):733-748; 11. Coelho T et al. Neurology. 2012;79:785-92; 12. Berk JL et al. JAMA. 2013;310:2658-67

# Patisiran Phase 3 APOLLO Study Results

## Study Design, Baseline Demographics and Characteristics



	APOLLO Population (N=225)			
	Placebo (N=77)		Patisiran (N=148)	
<b>Median Age, years (range)</b>	63 (34-80)		62 (24-83)	
<b>Gender, male</b>	58 (75.3)		109 (73.6)	
<b>TTR Genotype, n (%)</b>	<b>V30M:</b> 40 (51.9)		<b>V30M:</b> 56 (37.8)	
<b>NIS, mean (min, max)</b>	57 (7, 125.5)		60.5 (6, 141.6)	
<b>FAP Stage, n (%)</b>	1: 37 (48.1) 2: 39 (50.6) 3: 1 (1.3)		1: 67 (45.3) 2: 81 (54.7)	
<b>PND Score, n (%)</b>	I: 20 (26) II: 23 (29.9)	III A: 22 (28.6) III B: 11 (14.3) IV: 1 (1.3)	I: 36 (24.3) II: 43 (29.1)	III A: 41 (27.7) III B: 28 (18.9)

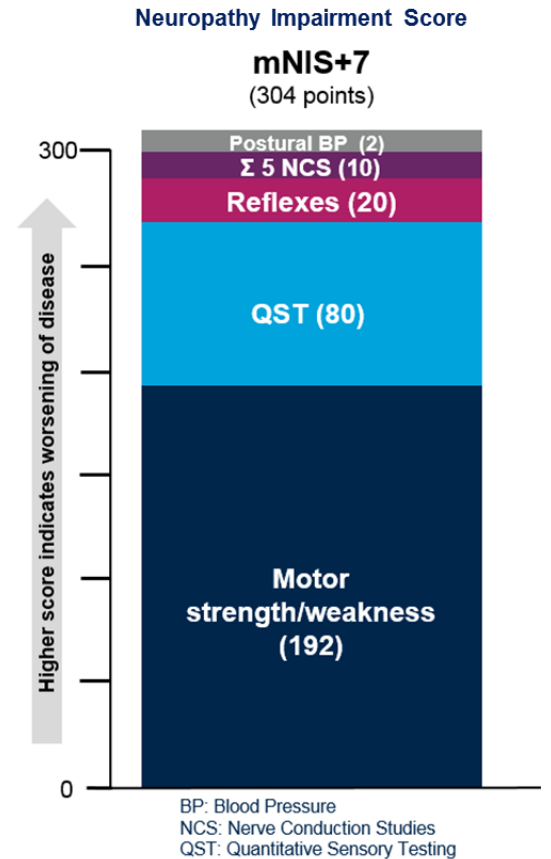
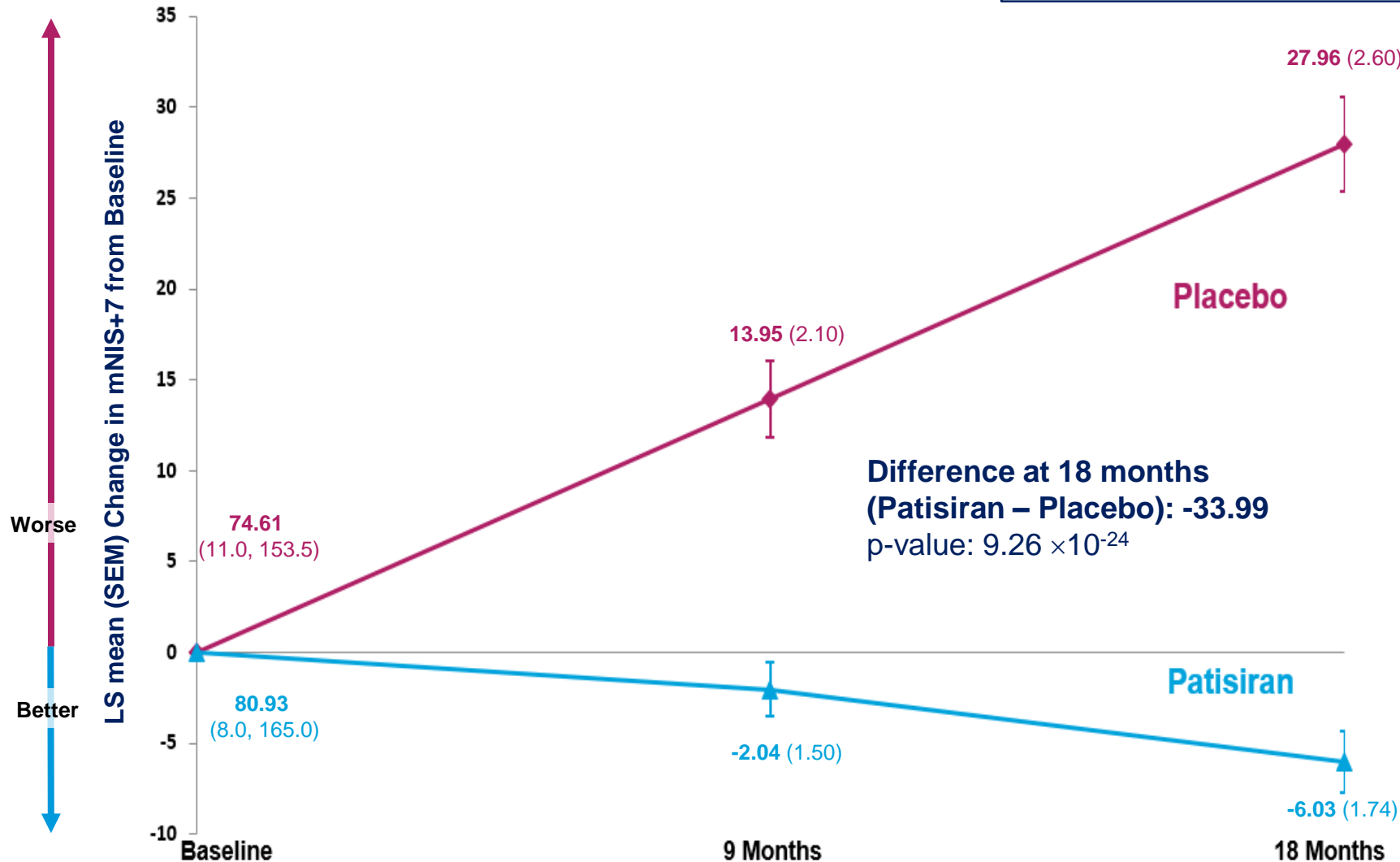
†Stratification factors for randomization include: neuropathy impairment score (NIS: < 50 vs. ≥ 50), early onset V30M (< 50 years of age at onset) vs. all other mutations (including late onset V30M), and previous tetramer stabilizer use (tafamidis or diflunisal) vs. no previous use.

\*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). COMPASS-31, composite autonomic symptom score-31; EQ-5D-5L, EuroQoL 5 dimensions-5L; mBMI, modified body mass index; mNIS+7, modified neuropathy impairment scale +7; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; OLE, open-label extension; q3W, every 3 weeks; R-ODS; Rasch-built overall disability scale; Adams D et al. BMC Neurol 2017;17(1):181

# Patisiran Phase 3 APOLLO Study Results

mNIS+7: Change from Baseline

56.1% of patients in the patisiran group demonstrated improvement in mNIS+7 compared to 3.9% of patients on placebo (odds ratio: 39.9; p=1.82 x 10<sup>-15</sup>; improvement defined as <0 point increase from baseline to 18 months)

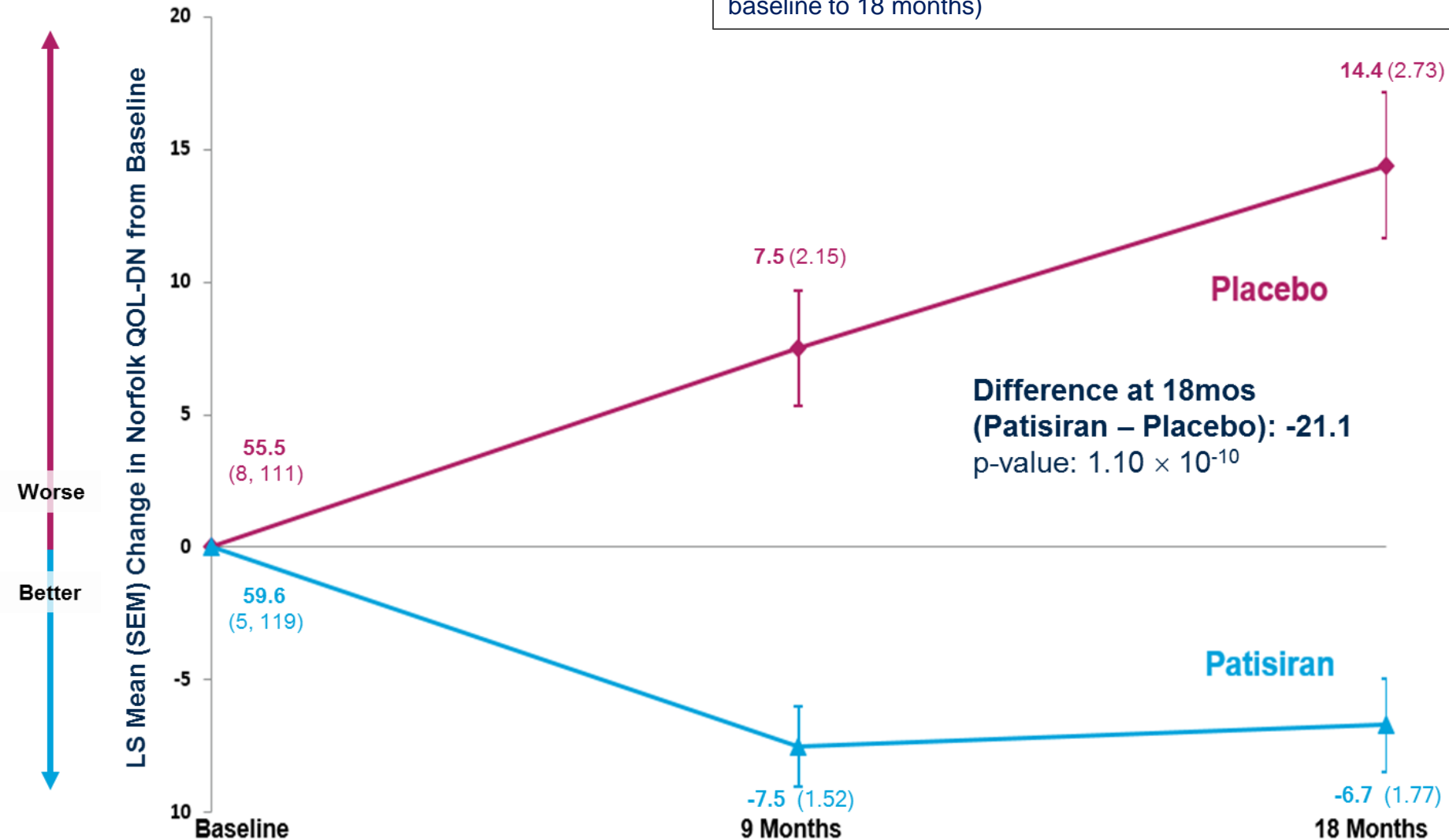


mNIS+7, modified neuropathy impairment score + 7; LS, least squares; SEM, standard error of the mean; mNIS+7 reference range: 0-304 points  
Data previously presented at the American Academy of Neurology (AAN) 2018; April 2018, Los Angeles, CA, USA

# Patisiran Phase 3 APOLLO Study Results

Norfolk QOL-DN: Change from Baseline

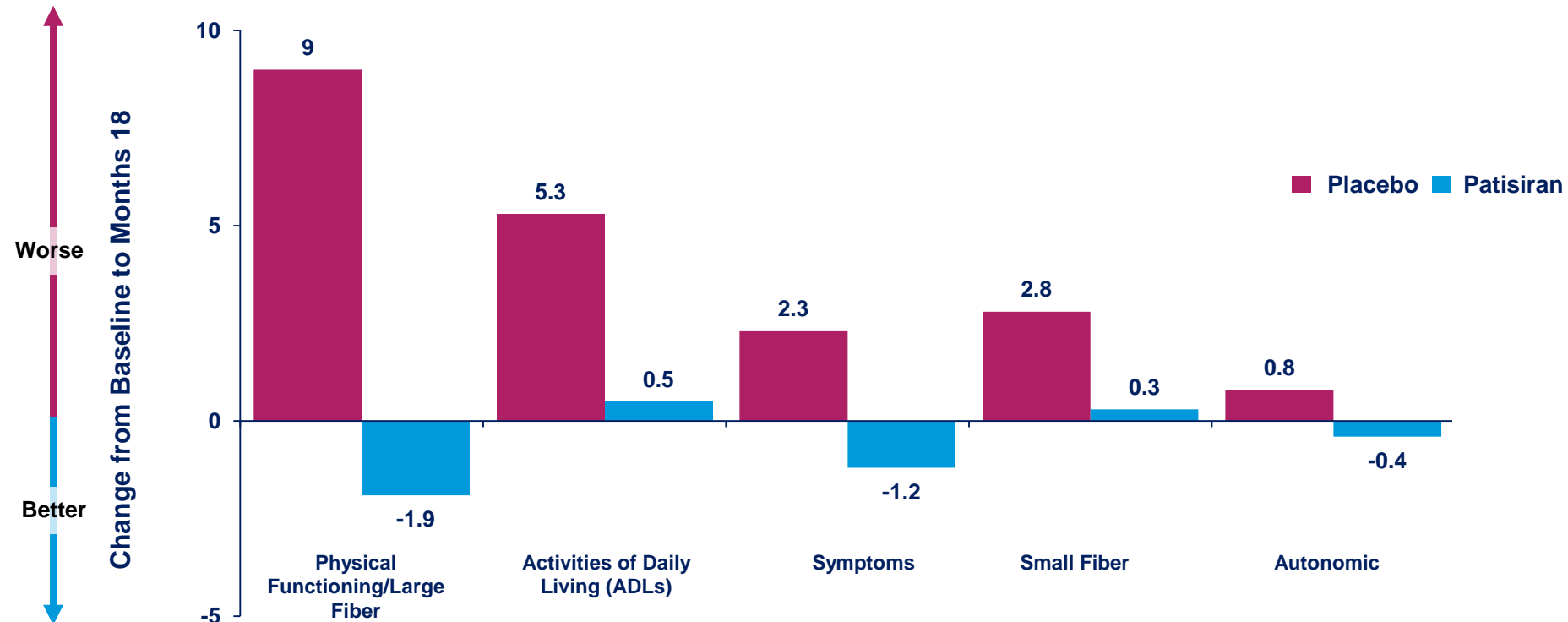
51.4% of patients in the patisiran group demonstrated improvement in Norfolk QOL-DN compared to 10.4% of patients on placebo (Odds ratio: 10.0;  $p=1.95 \times 10^{-10}$ ; improvement defined as  $<0$  point increase from baseline to 18 months)



# Patisiran Phase 3 APOLLO Study Results

## Norfolk QOL-DN: Change from Baseline in Individual Domains

- Patisiran demonstrated improvement relative to placebo across all domains of the Norfolk QOL-DN
- Improvement compared to baseline was observed in physical functioning/large fiber, symptoms, and autonomic domains
- This improvement in QOL at 18 months in patients on patisiran was related to strength, digestive health, ability to perform everyday activities, and steadiness on their feet



# 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)

No deaths considered related to study drug

- Causes of death consistent with natural history

Majority of AEs were mild or moderate in severity

- Peripheral edema
  - Decreased over time
  - Did not result in any treatment discontinuations
- Infusion-related reactions (IRRs)
  - Majority mild in severity
  - Decreased over time
  - 1 patient discontinued treatment

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)	<b>44 (29.7)</b>
Infusion related reaction (IRR)	7 (9.1)	<b>28 (18.9)</b>
Fall	<b>22 (28.6)</b>	25 (16.9)
Constipation	13 (16.9)	22 (14.9)
Nausea	<b>16 (20.8)</b>	22 (14.9)
Dizziness	11 (14.3)	19 (12.8)
Urinary tract infection	<b>14 (18.2)</b>	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	<b>11 (14.3)</b>	5 (3.4)
Anemia	<b>8 (10.4)</b>	3 (2.0)
Syncope	<b>8 (10.4)</b>	3 (2.0)

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

# Patisiran Phase 3 APOLLO Study

## Summary

- hATTR amyloidosis is a multisystem, progressive, debilitating, life-threatening disease with limited therapeutic options
- Patisiran treatment resulted in significant improvement in polyneuropathy relative to placebo and baseline at 18 months
  - 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
- Patisiran also improved quality of life relative to placebo and baseline
  - The improvement in QOL at 18 months in patients on patisiran was related to strength, digestive health, ability to perform everyday activities, and steadiness on their feet
  - In contrast, patients on placebo worsened across all domains at 18 months
- Patisiran showed an encouraging safety and tolerability profile
  - Frequency of deaths trended lower in the patisiran group versus placebo arm
  - 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
- 99% of eligible APOLLO patients enrolled into Global OLE study



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