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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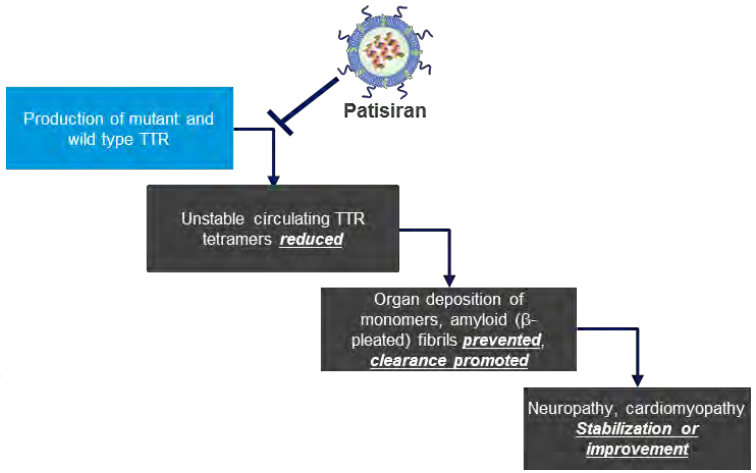
Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

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[1-5]
  - Median survival 4.7 years following diagnosis[6]; reduced survival (3.4 years) for patients presenting with cardiomyopathy[6-8]
- Multisystem disease with heterogeneous clinical presentation that includes sensory and motor, autonomic and cardiac symptoms[2,9,10]
  - 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[11] and certain other countries outside U.S.
    - Diflunisal (generic NSAID) showed positive Phase 3 data in NIH-sponsored study[12]
- 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



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Patisiran Phase 3 APOLLO Study Results

Study Design, Baseline Demographics and Characteristics

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Patient Population
- hATTR amyloidosis with documented TTR mutation
- Neurological impairment score (NIS) of 5-130
- Prior tetramer stabilizer use permitted

ClinicalTrials.gov Identifier: NCT01960348

2:1 RANDOMIZATION†

Patisiran
0.3 mg/kg IV q3w*

or

Placebo
IV q3W*

Primary Endpoint
- Change in mNIS+7 from baseline at 18 months

Secondary Endpoints
- Norfolk QOL-DN (quality of life)
- NIS-weakness (muscle weakness)
- R-ODS (disability)
- 10-meter walk (gait speed)
- mBMI (nutritional status)
- COMPASS-31 (autonomic symptoms)

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

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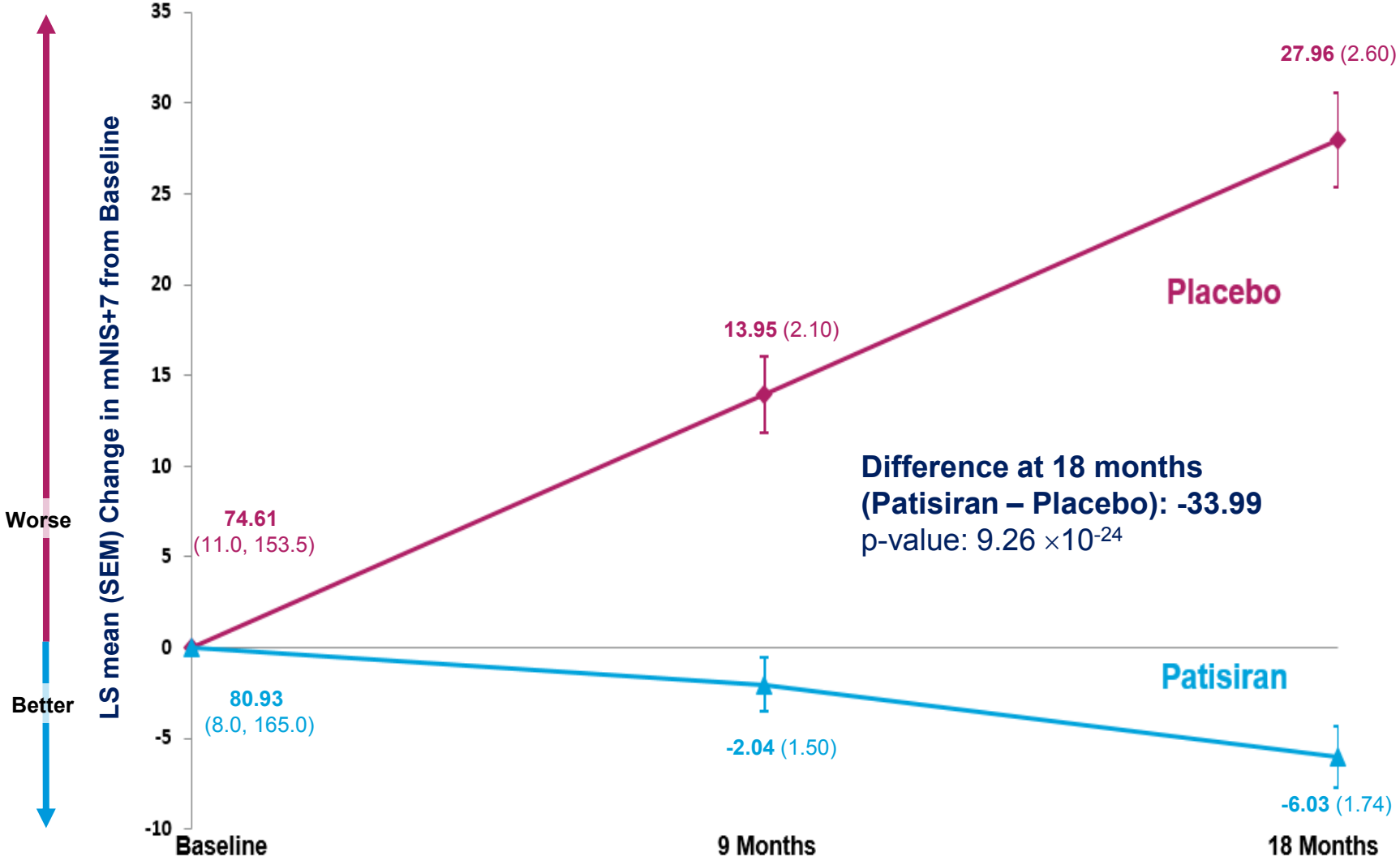
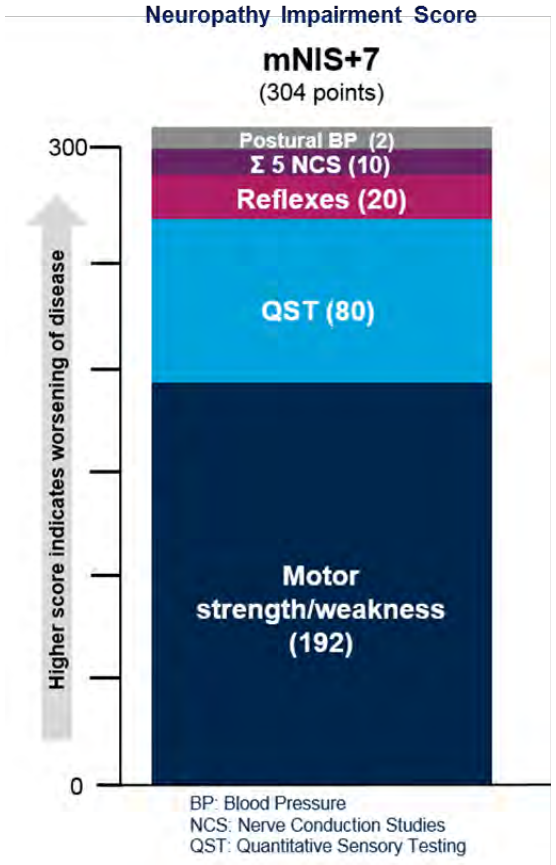
Patisiran Phase 3 APOLLO Study Results

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^{-15}; improvement defined as <0 point increase from baseline to 18 months)



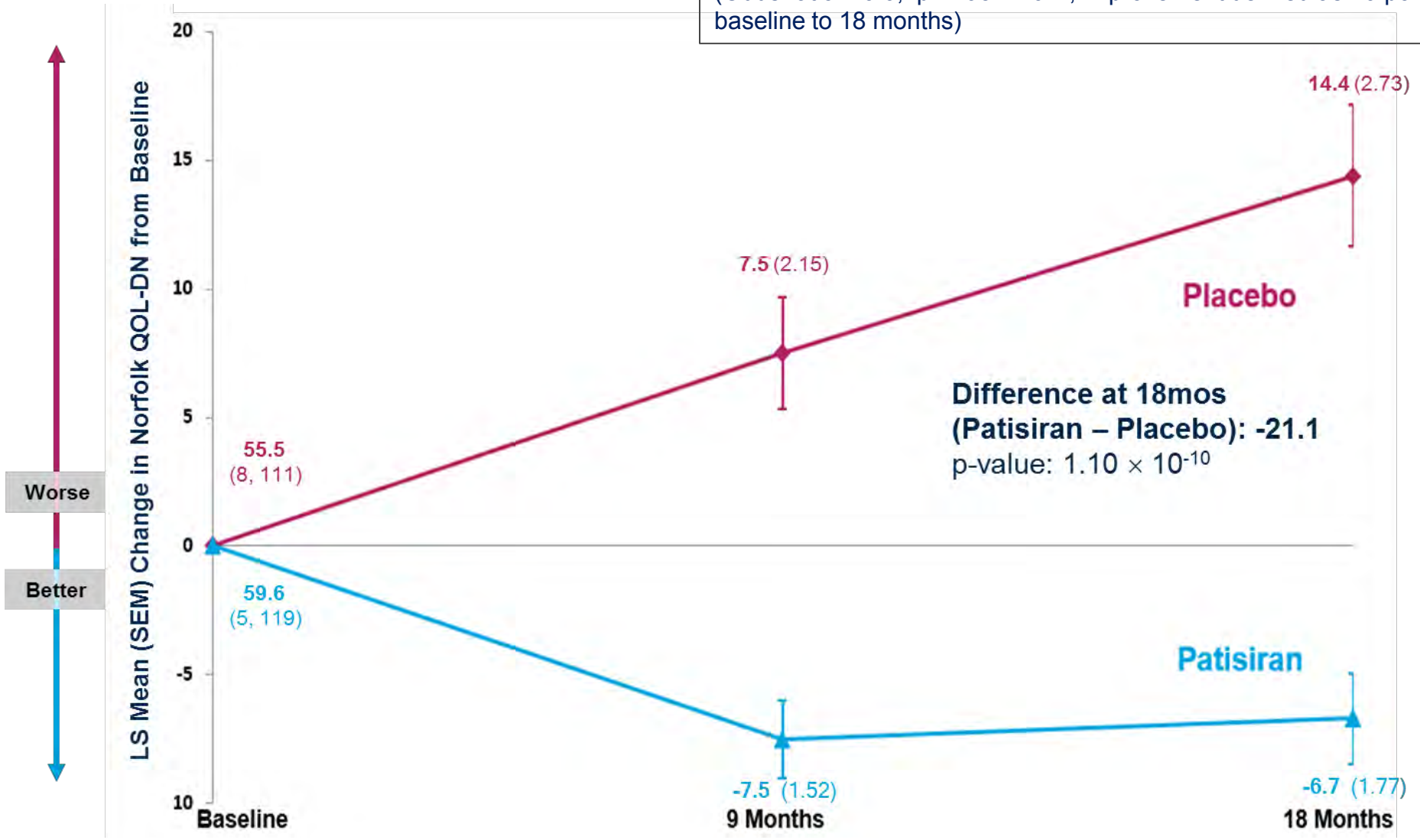


mNIS+7, modified neuropathy impairment score + 7; LS, least squares; SEM, standard error of the mean; mNIS+7 reference range: 0-304 points
Data previously presented at the American Academy of Neurology (AAN) 2018; April 2018, Los Angeles, CA, USA

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 x 10^{-10}; improvement defined as <0 point increase from baseline to 18 months)



LS, least squares; Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; SEM, standard error of the mean; Norfolk QOL-DN reference range: -4 – 136
Data previously presented at the American Academy of Neurology (AAN) 2018; April 2018, Los Angeles, CA, USA

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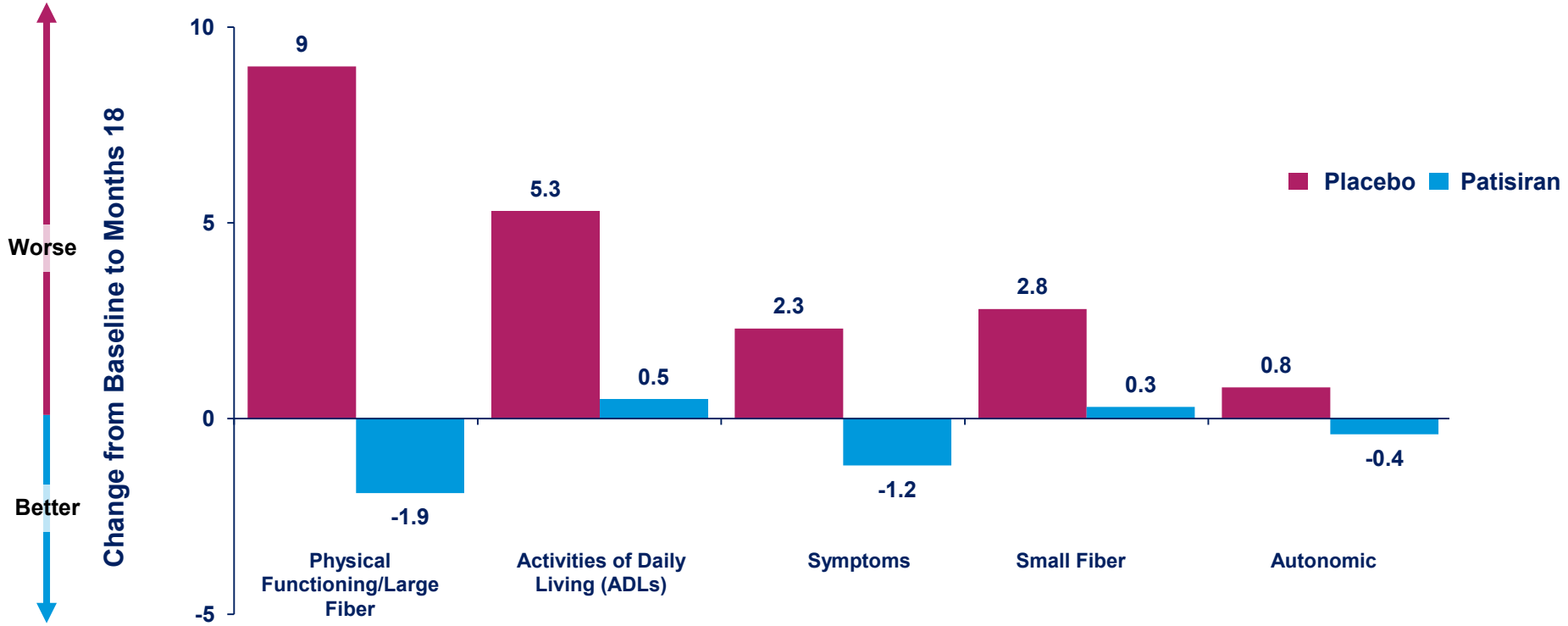
Patisiran Phase 3 APOLLO Study Results

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



Norfolk QOL-DN, Norfolk quality of life-diabetic neuropathy questionnaire; QOL, quality of life

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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)	**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

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

QOL, Quality of Life; IRRs, infusion related reactions; OLE, open label extension

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