Impact of Patisiran on Activities of Daily Living and Functional Status in hATTR Amyloidosis

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Disclosures

- Amanda Peltier has received personal compensation from Alnylam, Akcea, CSL Behring, and Catalyst; for serving on a Scientific Advisory or Data Safety Monitoring board for Akcea, Alnylam, CSL Behring, and Catalyst; and for serving on a Speakers Bureau for Akcea and CSL Behring; Vanderbilt University Medical Center has received research support from NIH

Background

Hereditary Transthyretin-Mediated (hATTR) Amyloidosis, Also Known as ATTRv Amyloidosis

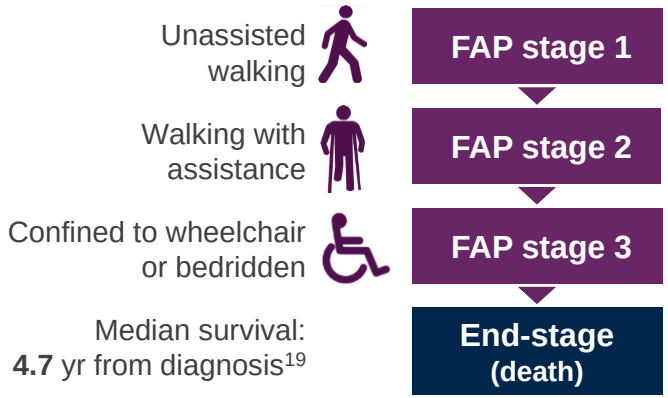
- **Rare, rapidly progressive, debilitating, and potentially fatal disease caused by a variant in the transthyretin (*TTR*) gene** that results in multisystem accumulation of amyloid fibrils (e.g., in nerves, heart, and gastrointestinal tract) and **subsequent dysfunction across multiple organs and tissues**[1–5]
  - Majority of patients develop a **mixed phenotype** of both polyneuropathy and cardiomyopathy[6–9]
- Patients experience increasingly impaired functional status, **declining ability to perform activities of daily living** (ADLs), and decreased QOL, with significant disability and loss of physical function at later stage disease as evidenced by the disease's ambulatory staging systems (i.e., FAP stage and PND score)[10–12]

Patisiran

- Lipid nanoparticle-delivered **RNAi therapeutic** that reduces serum TTR levels by inhibiting hepatic synthesis of the disease-causing variant and wild-type TTR proteins
- Approved in >30 countries for the treatment of hATTR amyloidosis with polyneuropathy[a,13–18]

Objective

- To describe the impact of patisiran on ADL and functional status in the Phase 3 APOLLO study



[a]Specific indications vary by country/region

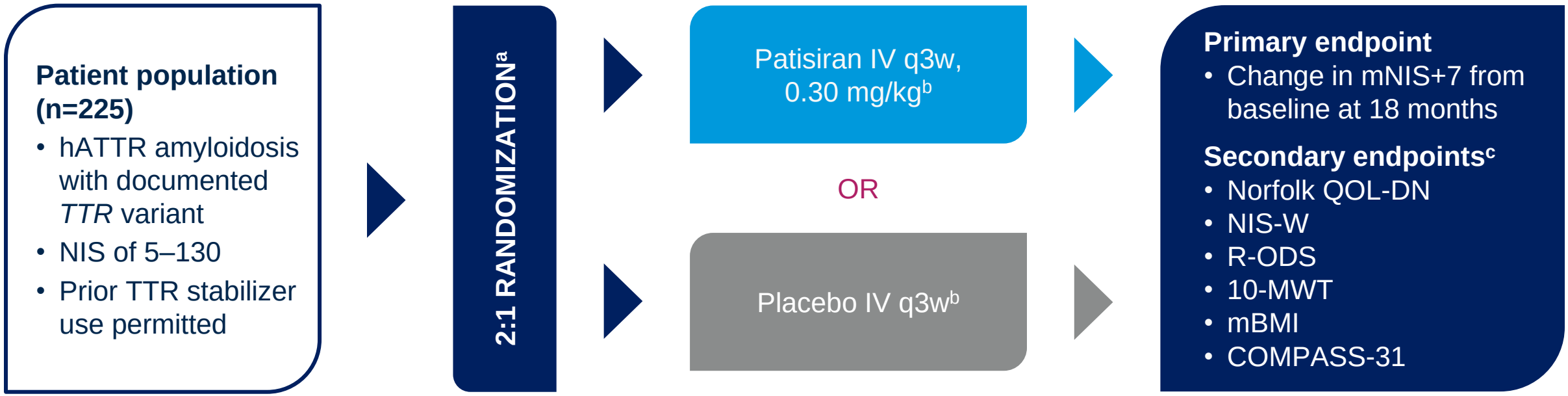
ADL, activities of daily living; ATTRv, hereditary transthyretin (v for variant); FAP, familial amyloid polyneuropathy; hATTR, hereditary transthyretin-mediated; PND, polyneuropathy disability score; QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin

1. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 2. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 3. Adams et al. *Neurology* 2015;85:675–82; 4. Damy et al. *J Cardiovasc Transl Res* 2015;8:117–27; 5. Hawkins et al. *Ann Med* 2015;47:625–38; 6. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 7. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 8. Adams et al. *N Engl J Med* 2018;379:11–21; 9. Benson et al. *N Engl J Med* 2018;379:22–31; 10. Adams. *Ther Adv Neurol Disord* 2013;6:129–39; 11. Suhr et al. *J Intern Med* 1994;235:479–85; 12. Coutinho et al. In: Glenner, Costa, de Freitas, editors. Amyloid and Amyloidosis. Amsterdam: Excerpta Medica; 1980. pp. 88–98; 13. Alnylam Pharmaceuticals Inc. US prescribing information: ONPATTRO (patisiran) lipid complex injection, for intravenous use. 2020. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210922s007lbl.pdf (accessed March 11, 2021); 14. European Medicines Agency. Summary of product characteristics: Onpattro 2 mg/mL concentrate for solution for infusion. 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf (accessed March 11, 2021); 15. Alnylam Pharmaceuticals Inc. Alnylam announces approval in Japan of ONPATTRO® for the treatment of hereditary ATTR amyloidosis with polyneuropathy. 2019. Available from: https://investors.alnylam.com/press-release?id=23886 (accessed March 11, 2021); 16. Canadian Agency for Drugs and Technologies in Health. Patisiran. Available from: https://www.cadth.ca/patisiran (accessed March 11, 2021); 17. Abbreviated information for health care professionals for ONPATTRO 10mg/5ml, concentrate for solution for infusion (Version September 2019). Available from: https://www.swissmedic.ch/dam/swissmedic/de/dokumente/zulassung/swisspar/67304-Onpattro-01-SwissPAR-20191113.pdf.download.pdf/67304-Onpattro-01-SwissPAR-20191113.pdf (accessed March 11, 2021); 18. Alnylam Pharmaceuticals Inc. Alnylam Announces Approval in Brazil of ONPATTRO® for the Treatment of Hereditary ATTR Amyloidosis with Polyneuropathy. Available from: https://investors.alnylam.com/press-release?id=24606 (accessed March 11, 2021); 19. Swiecicki et al. *Amyloid* 2015; 22:121–31

Methods

Phase 3 APOLLO Study Design

- Randomized, placebo-controlled study of patisiran 0.3 mg/kg intravenous (IV) every 3 weeks (q3w) in patients with hATTR amyloidosis with polyneuropathy; primary efficacy and safety results have been reported previously[1]



[a]Stratification factors of randomization included NIS: <50 vs ≥50, early-onset V30M (<50 years of age at onset) vs all other mutations (including late-onset V30M), and previous TTR stabilizer use (tafamidis or diflunisal) vs no previous use.
[b]To reduce the likelihood of infusion-related reactions, patients received the following premedication or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen/paracetamol; H2 blocker (e.g., ranitidine or famotidine); and H1 blocker (e.g., diphenhydramine). [c]Evaluated change from baseline to 18 months for each endpoint
10-MWT, 10-meter walk test; COMPASS-31, Composite Autonomic Symptom Score: 31-item questionnaire; hATTR, hereditary transthyretin-mediated; IV, intravenous; mBMI, modified body mass index; mNIS+7, modified NIS+7; NIS, Neuropathy Impairment Score; NIS-W, NIS-Weakness; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; q3w, every 3 weeks; R-ODS, Rasch-built Overall Disability Scale; TTR, transthyretin
1. Adams et al. *N Engl J Med* 2018;379:11–21

Methods

ADL and Functional Status Assessments

- **R-ODS:** 24-item patient-completed survey assessing activity and social participation limitations using a linearly weighted scale
  - Range: 0–48 points, lower scores indicate greater disability[1]
  - R-ODS raw total scores were converted to Rasch person-location values (logits), a ruler that measures activity and social participation limitations[1]; mean logits by treatment group (patisiran and placebo) and visit were plotted with R-ODS item locations representing the hierarchy of difficulty in performing various activities
- **Norfolk QOL-DN ADL:** 5-item patient-completed domain of the Norfolk QOL-DN assessing the level of difficulty performing the following activities: fine finger movements, bathing/showering, dressing, getting on or off the toilet, using eating utensils
  - Range: 0–20 points, higher scores indicate worse ADL ability[2]
  - Mean score ± SE from baseline was computed by treatment group and visit
- **KPS scale:** 11-point functional impairment rating scale in which patients are classified from normal functioning to dead
  - Range 0–100%, lower scores indicate a lower ability to perform activities and a worse survival prognosis
  - Change from baseline to 18 months was computed by treatment group
- A post hoc analysis was performed to estimate the **odds of stabilization or improvement versus worsening** on each assessment from baseline to 18 months

ADL, activities of daily living; KPS, Karnofsky Performance Status; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; R-ODS, Rasch-built Overall Disability Scale; SE, standard error

1. van Nes SI et al. *Neurology* 2011;76:337–45; 2. Vinik et al. *J Diabetes Sci Technol* 2008;2:1075–86

Baseline Demographics and Disease Characteristics

- Baseline characteristics were similar between treatment groups
  - Mean R-ODS score was 29.7 points (mean logit 1.3), indicating patients had, on average, lost ability to perform activities with a difficulty level of walking and avoiding obstacles and traveling by public transportation
  - Mean Norfolk QOL-DN ADL was 8.1 points, showing patients had lost some ability to complete daily activities at baseline on average
  - Mean KPS at baseline demonstrated that about half of patients were able to carry on normal activities (KPS 80–100%); remaining patients were unable to work and required some assistance (KPS 50–70%); no patients were entirely unable to care for themselves (KPS 0–40%)

APOLLO Baseline Demographics and Disease Characteristics

Characteristic	Placebo (n=77)	Patisiran (n=148)
Median age, years (range)	63 (34–80)	62 (24–83)
Male, n (%)	58 (75.3)	109 (73.6)
Region, n (%)		
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)
Median years since diagnosis (range)	1.4 (0.0–16.5)	1.3 (0.0–21.0)
Genotype, n (%)		
V30M	40 (51.9)	56 (37.8)
Non-V30M	37 (48.1)	92 (62.2)
R-ODS		
Mean (SD)	29.8 (10.76)	29.7 (11.51)
Median	30.5	29.5
Norfolk QOL-DN ADL		
Mean (SD)	7.8 (6.03)	8.2 (6.12)
Median	7	8
KPS scale, n (%)		
100%	0	3 (2.0)
90%	10 (13.0)	16 (10.8)
80%	31 (40.3)	44 (29.7)
70%	14 (18.2)	36 (24.3)
60%	22 (28.6)	49 (33.1)
0–50%	0	0
Mean NIS[a] (range)	57.0 (7.0–125.5)	60.5 (6.0–141.6)

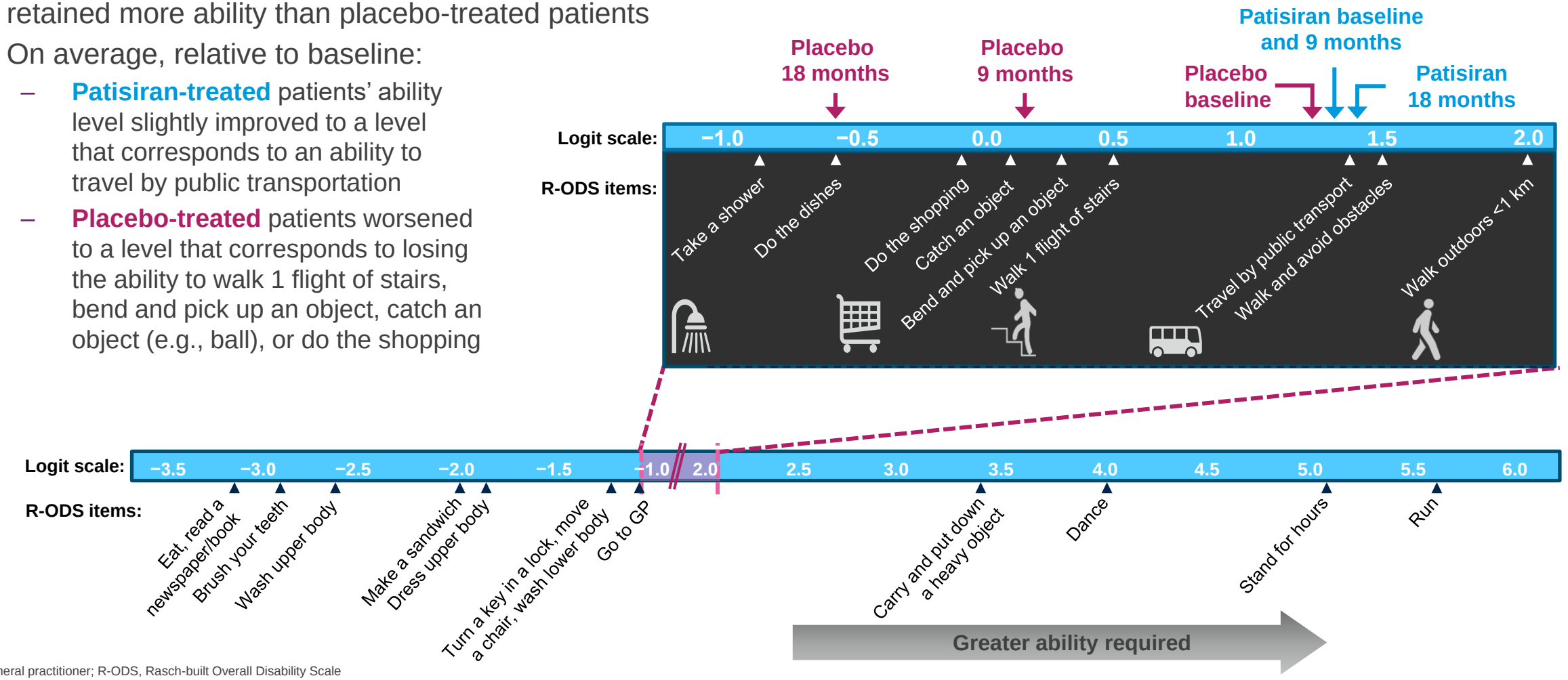
[a]NIS score of at least 5 was an inclusion criterion; NIS category (5–49, 50–130) was a stratification factor

ADL, activities of daily living; KPS, Karnofsky Performance Status; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; R-ODS, Rasch-built Overall Disability Scale; SD, standard deviation; TTR, transthyretin

Impact of Patisiran on Activity and Social Participation

Measured by R-ODS

- Over 18 months, patisiran-treated patients retained more ability than placebo-treated patients
- On average, relative to baseline:
  - **Patisiran-treated** patients' ability level slightly improved to a level that corresponds to an ability to travel by public transportation
  - **Placebo-treated** patients worsened to a level that corresponds to losing the ability to walk 1 flight of stairs, bend and pick up an object, catch an object (e.g., ball), or do the shopping

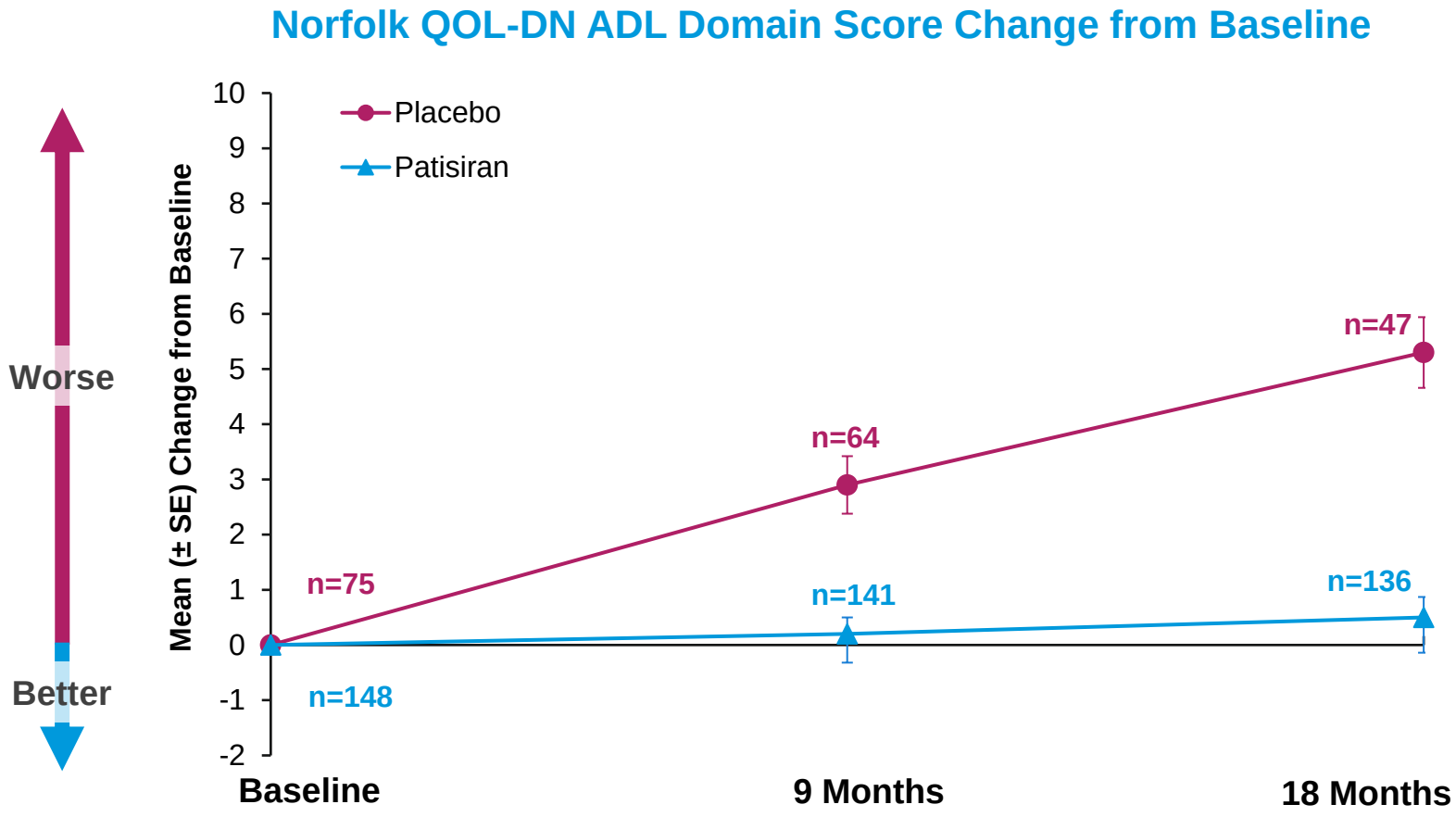


GP, general practitioner; R-ODS, Rasch-built Overall Disability Scale

Impact of Patisiran on Activities of Daily Living

Measured by Norfolk QOL-DN ADL Domain

- Patients who received patisiran retained greater ADL function compared with placebo
- Compared with baseline, Norfolk QOL-DN ADL scores worsened in patients in the placebo group, while patisiran-treated patients remained stable over 18 months

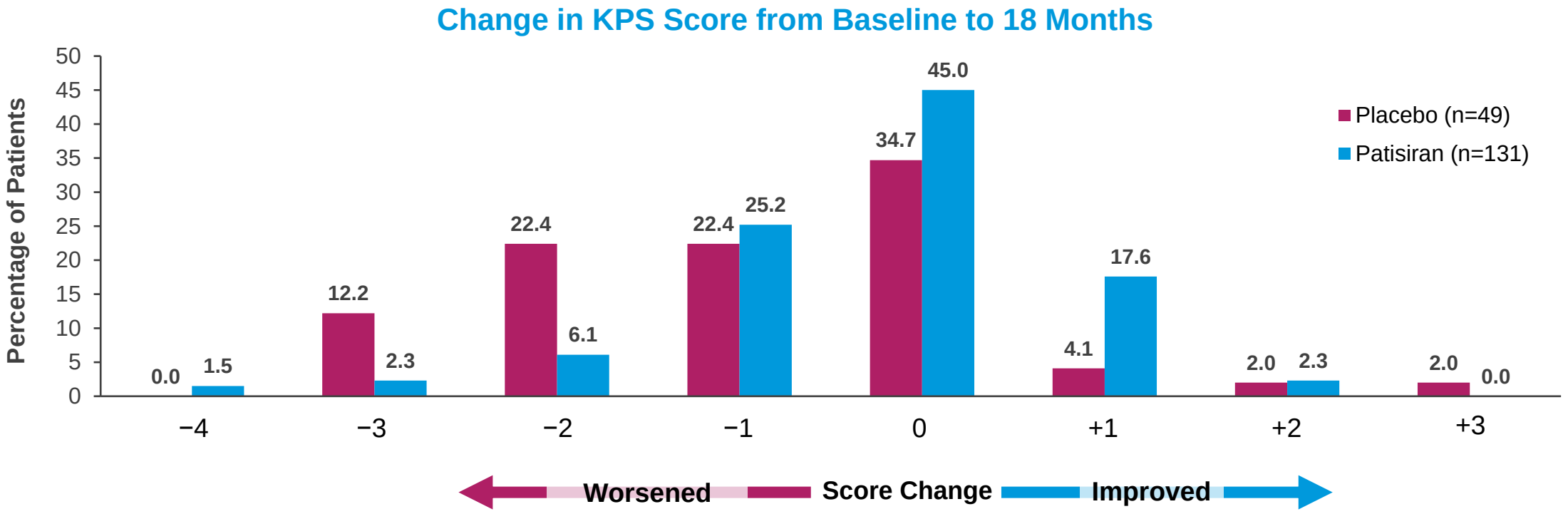


All summaries used observed (non-missing) data at each time point.
ADL, activities of daily living; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; SE, standard error

Impact of Patisiran on Functional Impairment

Measured by KPS

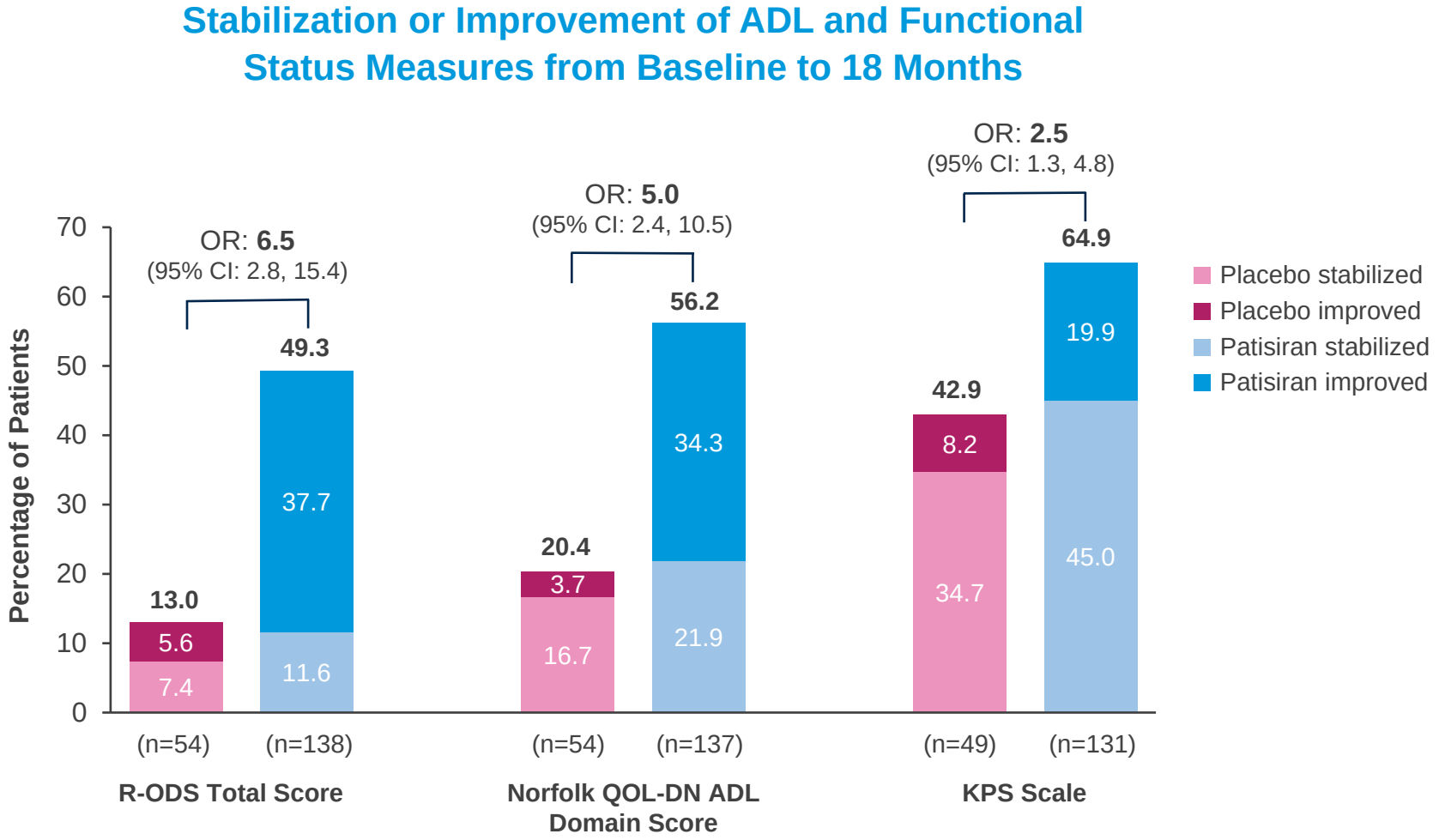
- After 18 months, a higher percentage of patisiran-treated patients retained or improved their baseline KPS score than placebo-treated patients



Range of KPS at baseline was 60–100 for patisiran-treated patients and 60–90 for placebo-treated patients. A higher score and positive change from baseline indicate improvement. All summaries used observed (non-missing) data at each time point
KPS, Karnofsky Performance Status

Odds Ratios for Stabilization or Improvement in R-ODS, Norfolk QOL-DN ADL Domain, and KPS

- After 18 months, the odds of stabilization or improvement in each functional status/ADL measure favored patisiran relative to placebo
- **Fifty percent or more of patisiran-treated patients remained stable or improved on at least one measure** of ADL and functional status
- In contrast, **the majority of placebo-treated patients worsened on each measure** after 18 months: R-ODS, 87.0%; Norfolk QOL-DN ADL domain, 79.6%; KPS score, 57.1%



All summaries used observed (non-missing) data at each time point

ADL, Activities of daily living; CI, confidence interval; KPS, Karnofsky Performance Status; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; OR, odds ratio; R-ODS, Rasch-built Overall Disability Scale

Conclusions

Summary

- Patients treated with patisiran, on average, improved in their level of function sufficient to travel by public transportation, while those treated with placebo lost some of their baseline abilities
- Patisiran-treated patients were more than twice as likely than placebo-treated patients to improve or stabilize in R-ODS, Norfolk QOL-DN ADL domain, and KPS; ADL and functional status stabilized or improved in approximately half or more of patisiran-treated patients
- In patients treated with placebo, ADL and functional status worsened, illustrating the progressive functional decline observed in the natural history of hATTR amyloidosis with polyneuropathy
- Patisiran has demonstrated the potential to mitigate the functional decline associated with the progressive polyneuropathy of hATTR amyloidosis and has improved daily functional ability in some patients

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ADL, activities of daily living; hATTR, hereditary transthyretin-mediated; KPS, Karnofsky Performance Status; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; R-ODS, Rasch-built Overall Disability Scale

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