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

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Background

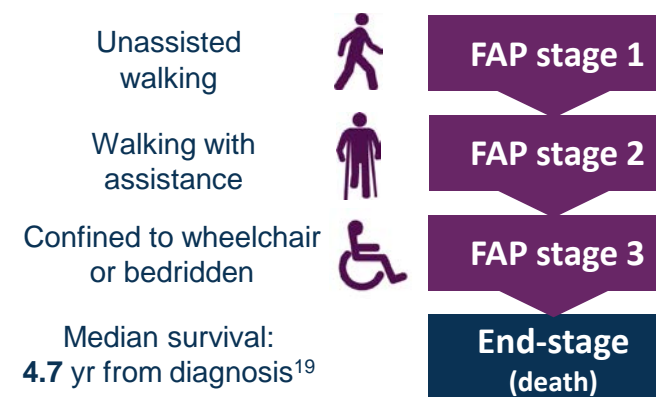## Hereditary Transthyretin-Mediated (hATTR) Amyloidosis, Also Known As ATTRv Amyloidosis

- **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 (wt) 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

Unassisted walking	FAP stage 1
Walking with assistance	FAP stage 2
Confined to wheelchair or bedridden	FAP stage 3
Median survival: **4.7** yr from diagnosis[19]	End-stage (death)

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 May 29, 2020); 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 February 13, 2020); 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 February 13, 2020); 16. Canadian Agency for Drugs and Technologies in Health. Available from: https://www.cadth.ca/patisiran (accessed February 13, 2020); 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 February 13, 2020); 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; 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]

Patient population (n=225)
- hATTR amyloidosis with documented *TTR* variant
- NIS of 5–130
- Prior TTR stabilizer use permitted

2:1 RANDOMIZATION[a]

Patisiran IV q3w, 0.30 mg/kg[b]

OR

Placebo IV q3w[b]

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

Secondary endpoints[c]
- Norfolk QOL-DN
- NIS-W
- R-ODS
- 10-MWT
- mBMI
- COMPASS-31
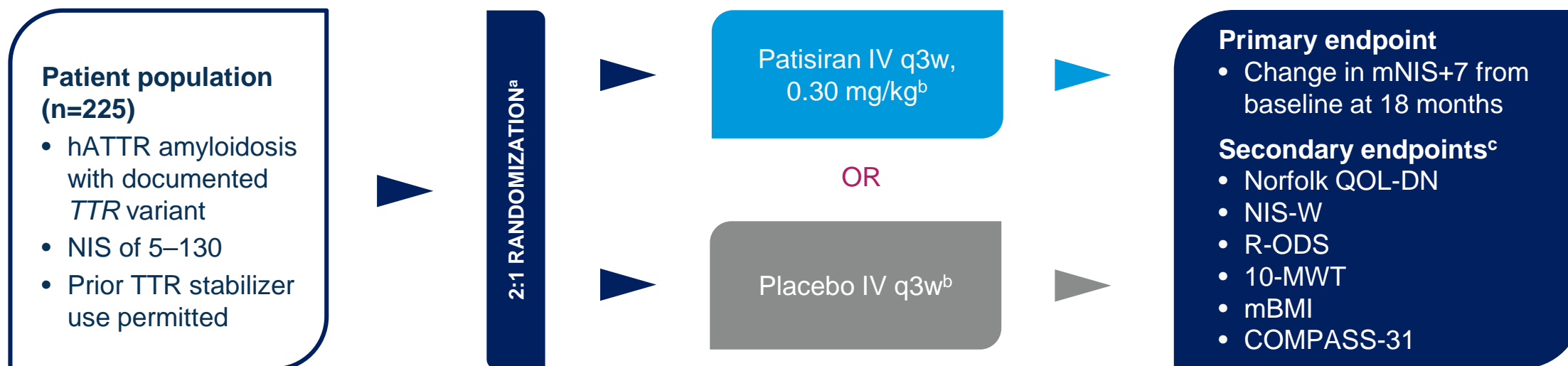
[a]Stratification factors of randomization included NIS: <50 vs ≥50, early-onset V30M (<50 years of age at onset) vs all other mutations (including late-onset V30M), and previous TTR stabilizer use (tafamidis or diflunisal) vs no previous use. [b]To reduce likelihood of infusion-related reactions, patients 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, Neuropathy Impairment Score-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%)
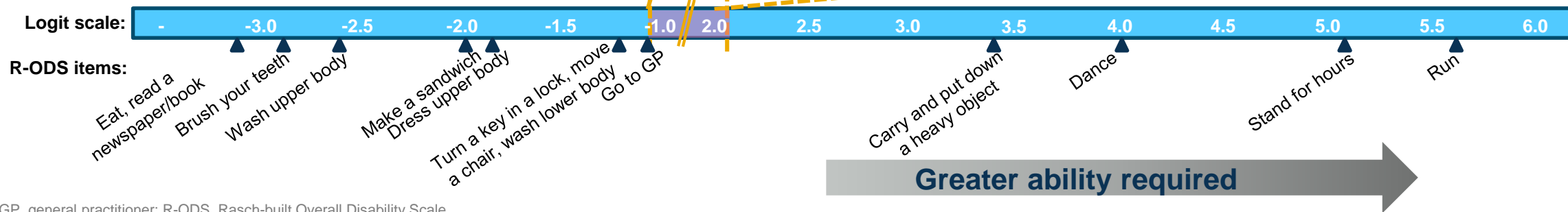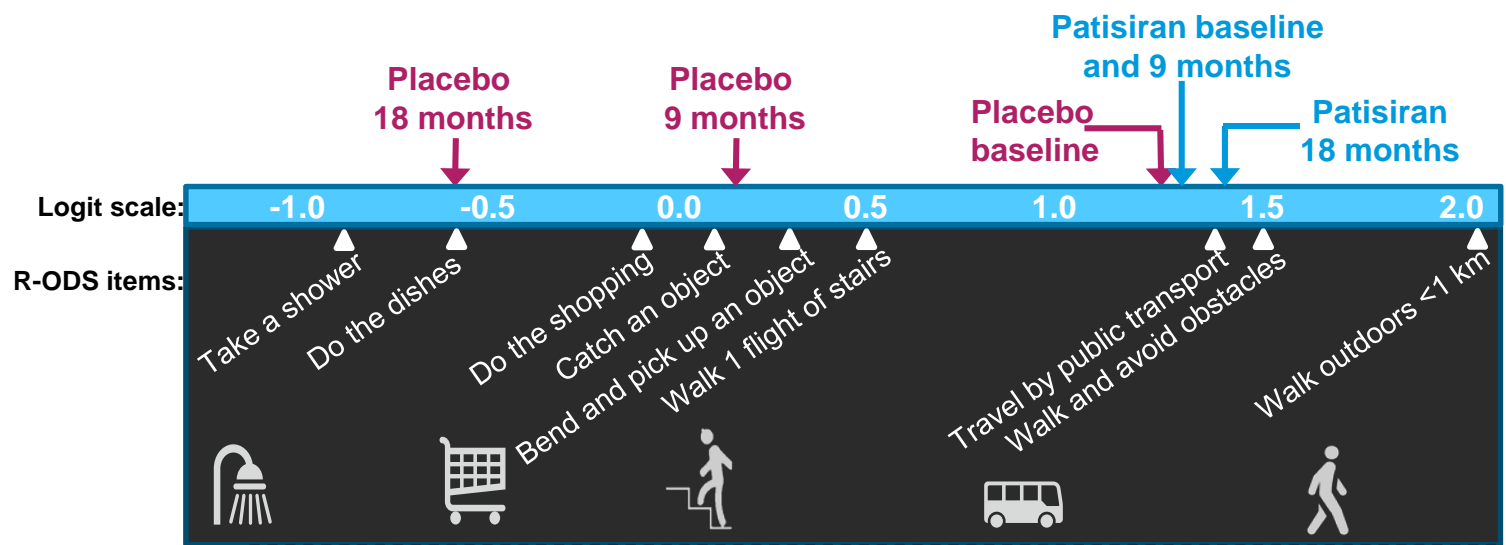
APOLLO Baseline Demographics and Disease

Characteristic	Placebo (n=77)	Patisiran (n=148)
Median age (range), years	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

Placebo 18 months

Placebo 9 months

Placebo baseline

Patisiran baseline and 9 months

Patisiran 18 months

Logit scale: -1.0 -0.5 0.0 0.5 1.0 1.5 2.0

R-ODS items:
Take a shower
Do the dishes
Do the shopping
Catch an object
Bend and pick up an object
Walk 1 flight of stairs
Travel by public transport
Walk and avoid obstacles
Walk outdoors <1 km

Logit scale: - -3.0 -2.5 -2.0 -1.5 -1.0 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0

R-ODS items:
Eat, read a newspaper/book
Brush your teeth
Wash upper body
Make a sandwich
Dress upper body
Turn a key in a lock, move a chair, wash lower body
Go to GP
Carry and put down a heavy object
Dance
Stand for hours
Run

Greater ability required

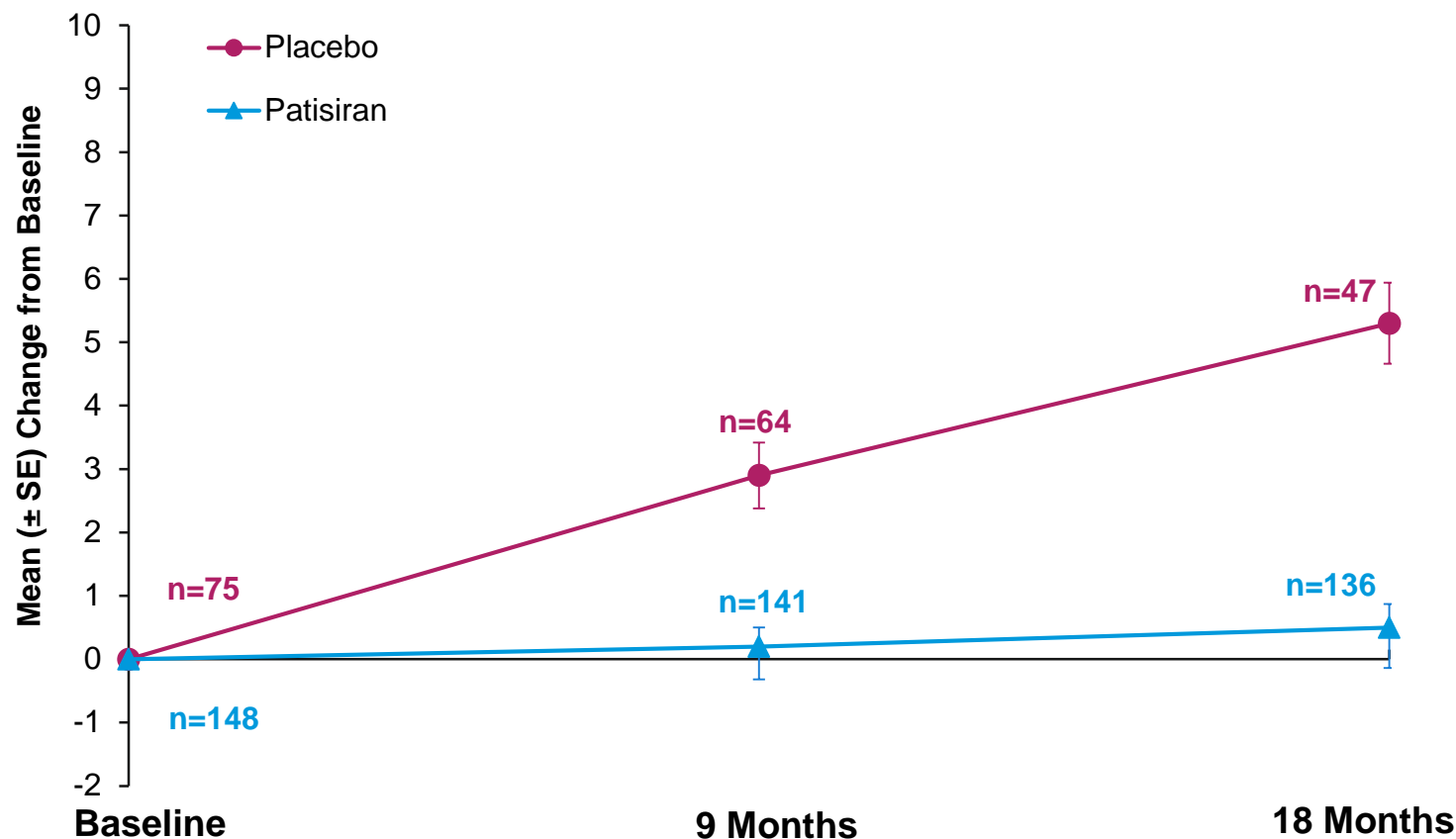GP, general practitioner; R-ODS, Rasch-built Overall Disability Scale

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

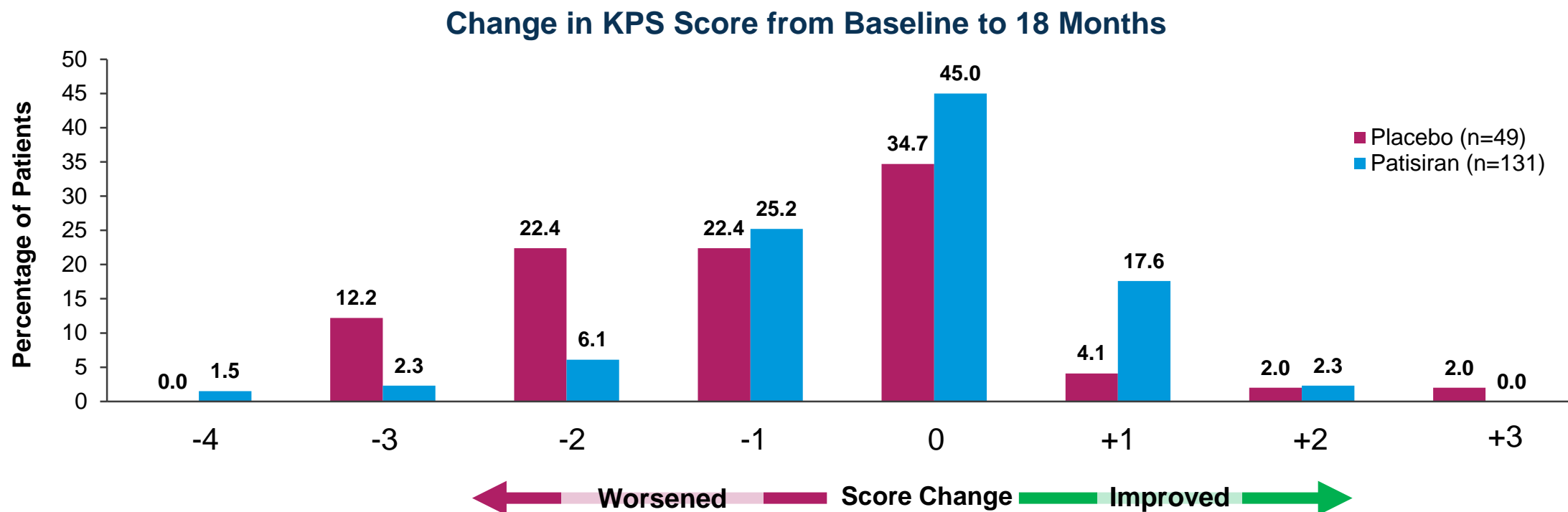**Norfolk QOL-DN ADL Domain Score Change from Baseline**

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

Change in KPS Score from Baseline to 18 Months

KPS, Karnofsky Performance Status. Range of KPS at baseline was 60-100 for patisiran-treated patients, 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
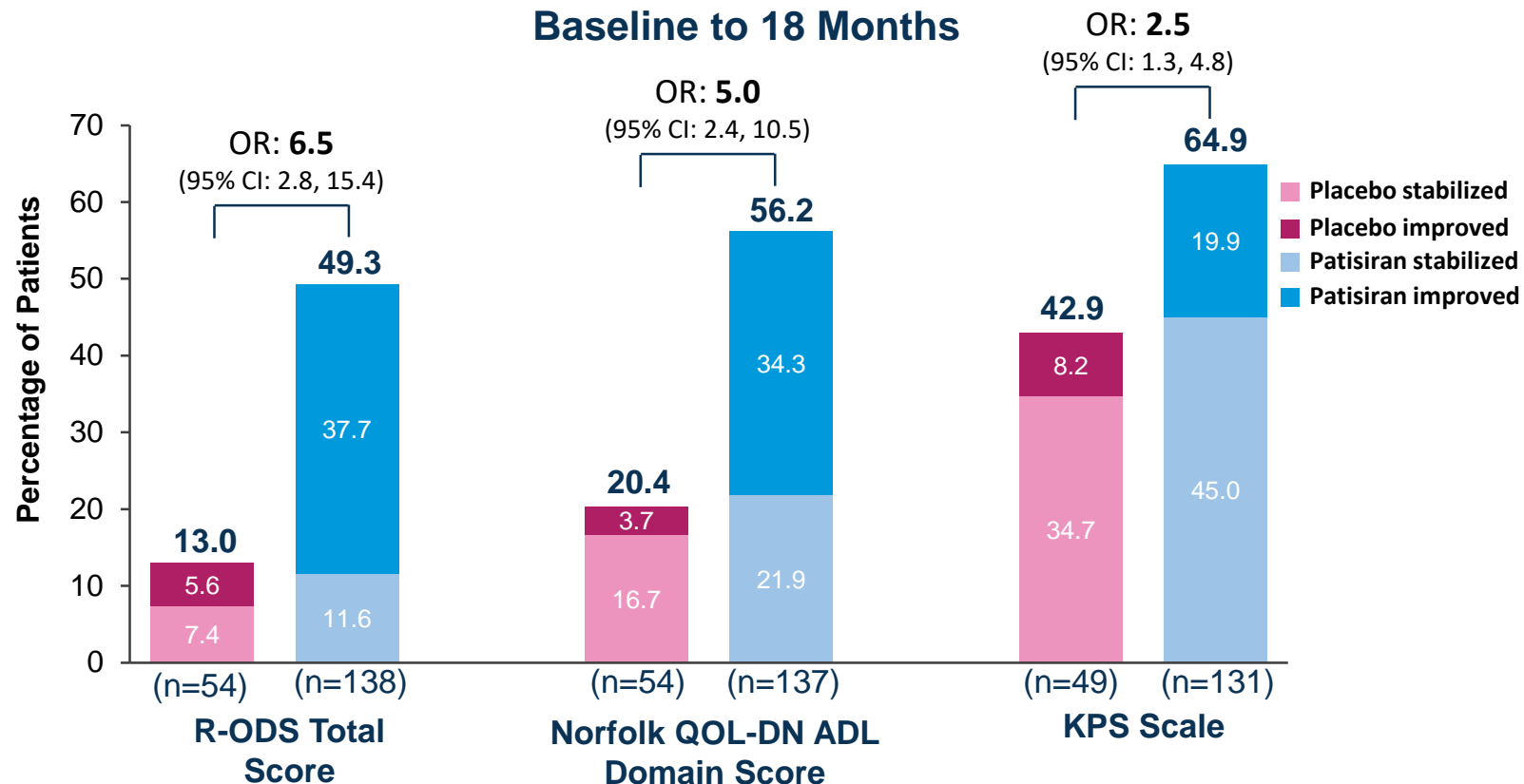
Odds Ratios for Stabilization or Improvement in R-ODS, Norfolk QOL-DN ADL Domain, and KPS

- 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%

Stabilization or Improvement of ADL and Functional Status Measures from Baseline to 18 Months

All summaries used observed (non-missing) data at each time point
ADL. Activities of daily living; KPS, Karnofsky Performance Status; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; R-ODS, Rasch-built Overall Disability Scale

Conclusion

- 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

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

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