Impact of Patisiran on Health Status and Quality of Life in Patients with Transthyretin Cardiac Amyloidosis

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Background and Rationale

ATTR Amyloidosis

- A progressive and fatal disease caused by accumulation of TTR amyloid fibrils in multiple organs and tissues[1–4]
- Disease progression has a major impact on patients' functional capacity, health status, and quality of life[5–7]

Patisiran

- An IV-administered RNAi therapeutic approved for the treatment of ATTRv amyloidosis with polyneuropathy in the US and EU[8,9]
- Data in patients with ATTR amyloidosis suggest the potential for patisiran to improve cardiac manifestations and preserve functional capacity, health status, and quality of life[10–12]

Objective

- To further characterize the beneficial impact of patisiran on health status and quality of life in patients with ATTR cardiac amyloidosis in the APOLLO-B study (NCT03997383)

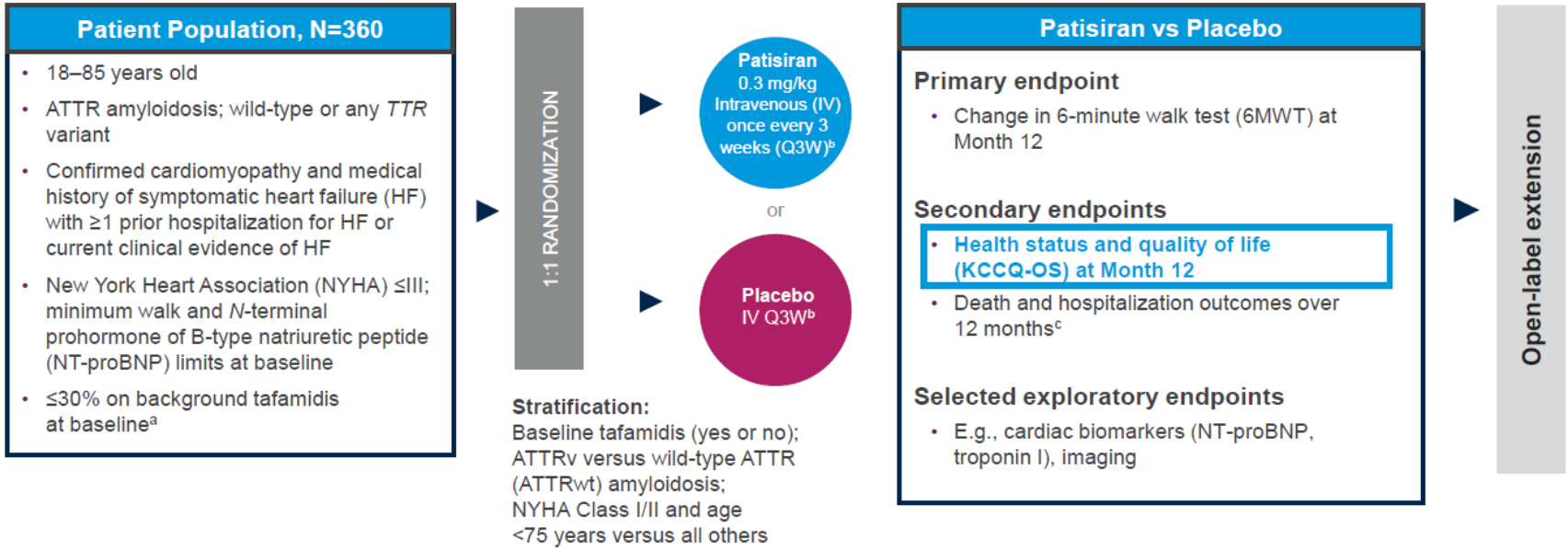
ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); IV, intravenous; RNAi, RNA interference; TTR, transthyretin. 1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 4. Sipe et al. *Amyloid* 2014;21:221–4; 5. Castano et al. *Heart Fail Rev* 2015;20:163–78; 6. Ruberg et al. *Am Heart J* 2012;164:222–8.e1; 7. Lane et al. *Circulation* 2019;140:16–26; 8. Food and Drug Administration 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf (accessed June 2023); 9. European Medicines Agency 2018. Available from: https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf (accessed June 2023); 10. Adams et al. *N Engl J Med* 2018;379:11–21; 11. Solomon et al. *Circulation* 2019;139:431–43; 12. Maurer et al. *Heart Failure Society of America (HFSA) 2022 Annual Meeting* (Poster 341).

Methods

Patisiran Phase 3 APOLLO-B Study

- APOLLO-B was a Phase 3, randomized, double-blind, placebo-controlled study of patisiran versus placebo in patients with ATTR cardiac amyloidosis (**Figure 1**)
- This post hoc analysis evaluated change from baseline to Month 12 in scores for KCCQ-OS, KCCQ Clinical Summary, and KCCQ domains and responses to individual questions

Figure 1. APOLLO-B Study Design



[a]Where tafamidis is available as local standard of care; receiving tafamidis treatment ≥6 months with disease progression in opinion of investigator. [b]To reduce likelihood of infusion-related reactions, patients receive following premedications or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen; H1 and H2 blockers. [c]Composite all-cause mortality, frequency of CV events, and change from baseline in 6MWT; composite all-cause mortality, frequency of all-cause hospitalizations, and urgent HF visits in patients not on tafamidis at baseline; composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in overall population. 6MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; CV, cardiovascular; H, histamine; HF, heart failure; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; Q3W, once every 3 weeks; TTR, transthyretin.

Baseline Demographic and Disease Characteristics

- A total of 359 patients received study drug in APOLLO-B (patisiran, n=181; placebo, n=178)
- Baseline demographics and disease characteristics were similar across the treatment groups (**Table 1**)
  - The majority of patients were male, had ATTRwt cardiac amyloidosis, and were in NYHA Class II
  - Overall, 25% of patients were receiving tafamidis at baseline

ATTRwt, wild-type transthyretin; NYHA, New York Heart Association.

Baseline Demographic and Disease Characteristics (cont'd)

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Patisiran (N=181)	Placebo (N=178)
Age, median (range), years	76 (47–85)	76 (41–85)
Male sex, n (%)	161 (89.0)	160 (89.9)
Race, n (%)		
White	138 (76.2)	140 (78.7)
Asian	23 (12.7)	15 (8.4)
Black or African American	16 (8.8)	15 (8.4)
ATTRwt amyloidosis, n (%)	144 (79.6)	144 (80.9)
Time since diagnosis of ATTR amyloidosis, median (range), years	0.8 (0–6)	0.4 (0–10)
Baseline tafamidis use, n (%)	46 (25.4)	45 (25.3)
NYHA Class, n (%)		
Class I	10 (5.5)	15 (8.4)
Class II	156 (86.2)	150 (84.2)
Class III	15 (8.3)	13 (7.3)

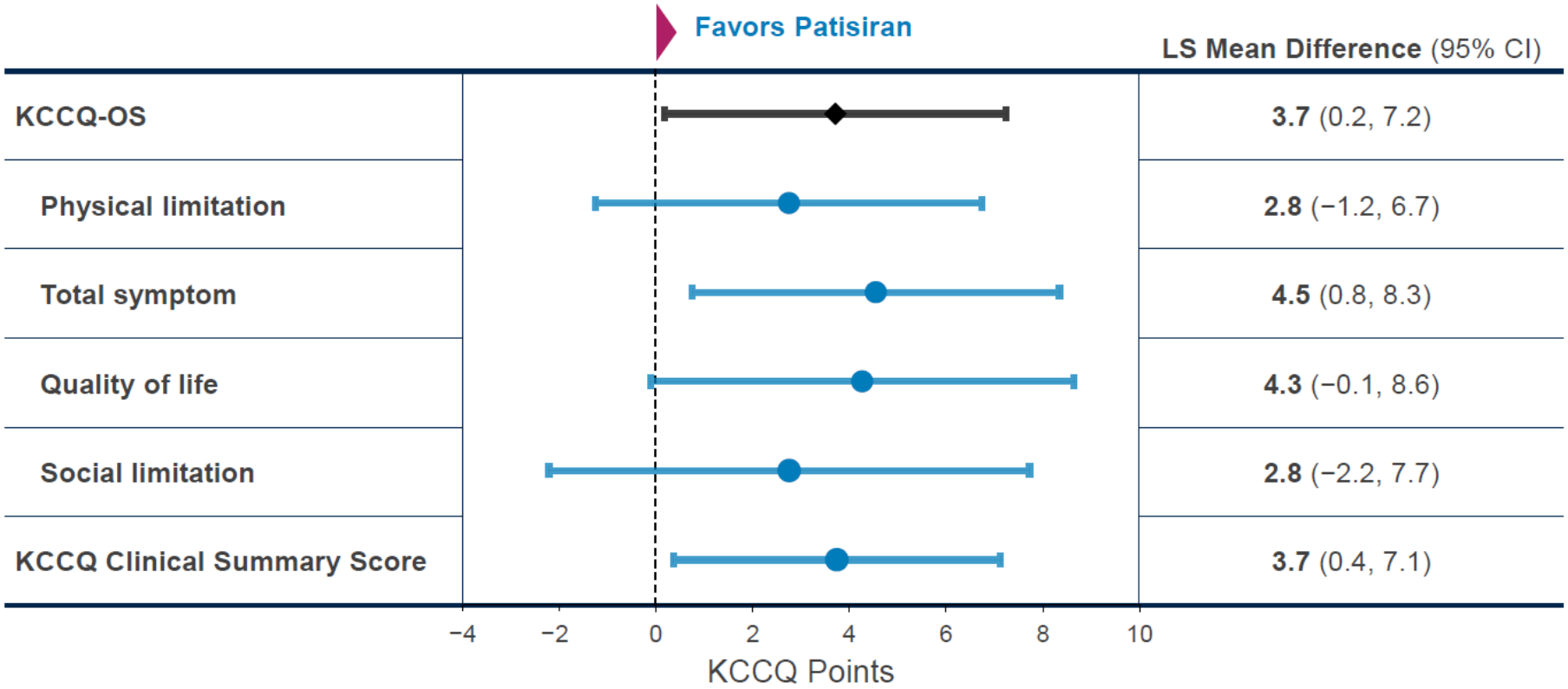
Characteristic	Patisiran (N=181)	Placebo (N=178)
ATTR amyloidosis stage[a], n (%)		
Stage 1	124 (68.5)	120 (67.4)
Stage 2	46 (25.4)	45 (25.3)
Stage 3	11 (6.1)	13 (7.3)
Polyneuropathy disability score, n (%)		
0: no impairment	96 (53.0)	109 (61.2)
I: preserved walking, with sensory disturbances	63 (34.8)	55 (30.9)
II: impaired walking without need for a stick or crutches	22 (12.2)	14 (7.9)
6MWT, m, median (IQR)	358.0 (295.0–420.0)	367.7 (300.0–444.3)
KCCQ-OS, points, mean (SD)	69.8 (21.2)	70.3 (20.7)
NT-proBNP level, ng/L, median (IQR)	2008 (1135–2921)	1813 (952–3079)
High-sensitivity troponin I level, ng/L, median (IQR)	64.0 (38.6–92.0)[b]	60.2 (38.2–103.1)[c]
eGFR, mL/min/1.73 m^2, median (IQR)	71.0 (58.0–83.0)	67.0 (51.0–84.0)

[a]Patients are stratified into prognostic categories using the serum biomarkers NT-proBNP and eGFR. Patients are categorized as follows: stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min/1.73 m^2; stage 2 (intermediate risk): all other patients not meeting criteria for stages 1 or 3; stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m^2. [b]n=174. [c]n=172. 6MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRwt, wild-type transthyretin; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Changes in KCCQ-OS Score and its Individual Components

- Patisiran demonstrated significant clinical benefit in health status and quality of life (KCCQ-OS) compared with placebo at Month 12 (LS mean difference 3.7 [95% CI 0.2, 7.2]; **Figure 2**)
  - The treatment benefit with patisiran was observed across all four domains of the KCCQ and the KCCQ Clinical Summary Score

Figure 2. LS Mean Difference between Patisiran and Placebo in Change from Baseline in KCCQ-OS, the Four Domains of the KCCQ, and KCCQ Clinical Summary Score at Month 12

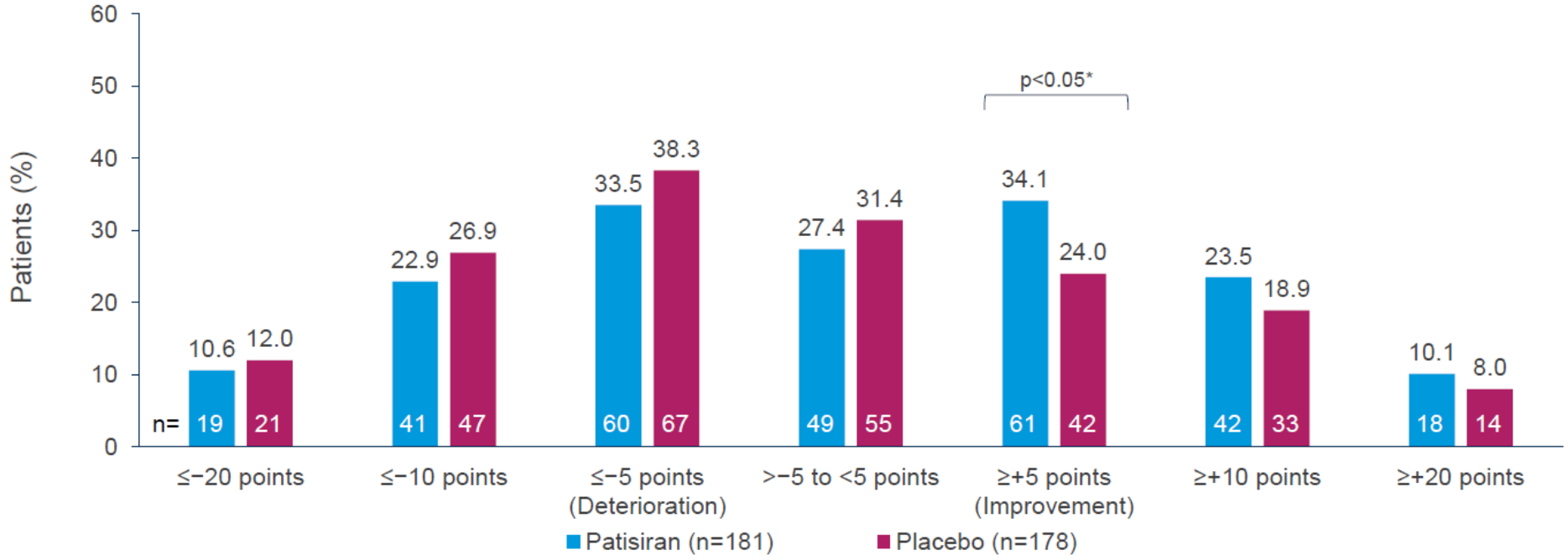


CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS, least squares.

Changes in KCCQ-OS Score and its Individual Components (cont'd)

- More patisiran-treated patients achieved improvements of ≥+5, ≥+10, and ≥+20 points in KCCQ-OS score at Month 12 compared with placebo (**Figure 3**)
  - Significantly more patisiran- than placebo-treated patients improved by ≥+5 points ($p<0.05$)
- More placebo-treated patients showed a deterioration of ≤−5, ≤−10, and ≤−20 points compared with patisiran

Figure 3. Proportion of Patients by Threshold of Change from Baseline to Month 12 in KCCQ-OS Score



*p-values were calculated using the Cochran–Mantel–Haenszel test stratified by baseline tafamidis use. KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary.

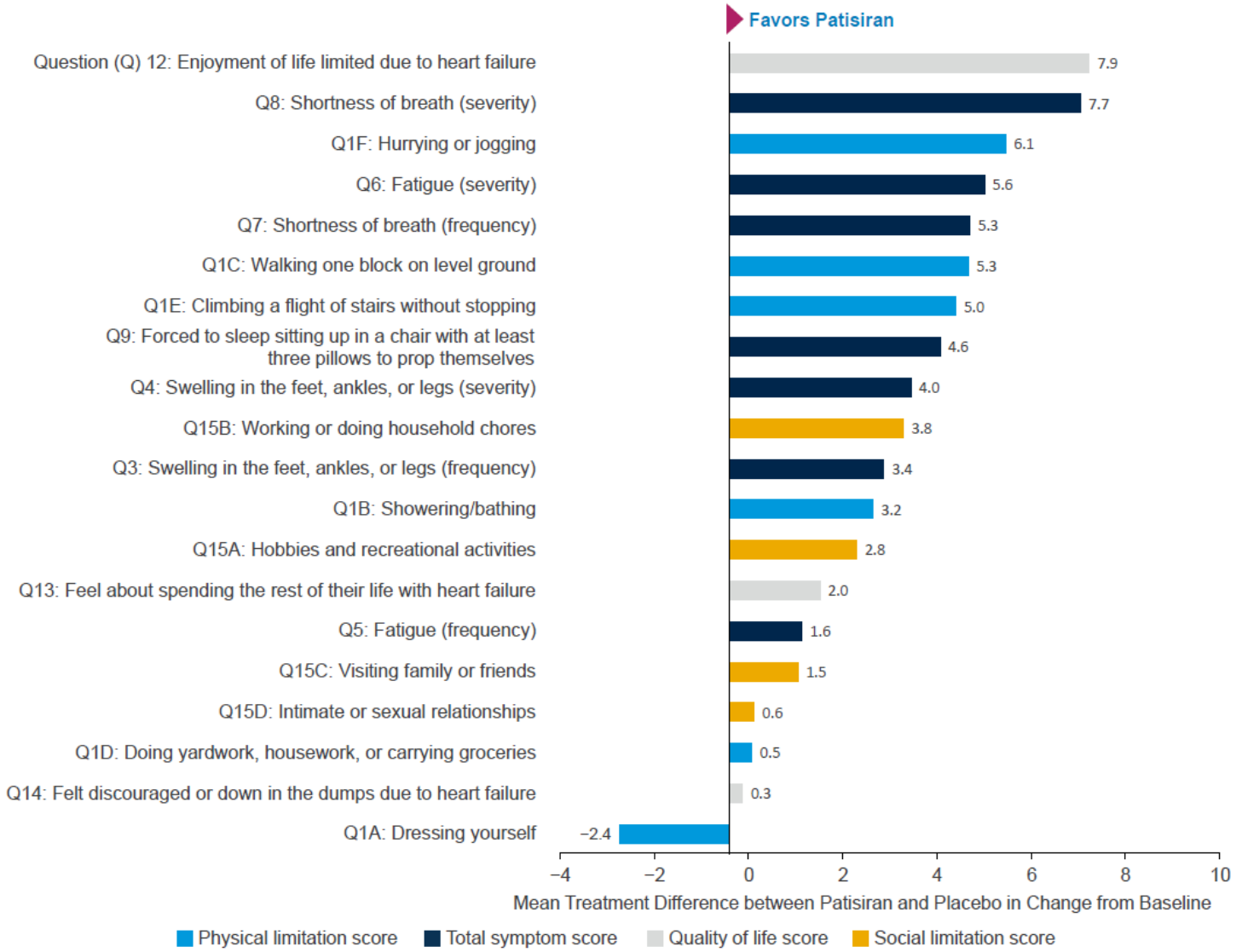
Treatment Effects across Individual Questions in the KCCQ-OS

- Treatment effects favoring patisiran were demonstrated across 19 of the 20 questions in the four KCCQ-OS components (**Figure 4**)
- Among the largest treatment effects observed were those related to walking and demanding physical activities, such as hurrying or jogging and climbing stairs, as well as shortness of breath and fatigue that limit exertion
- The greatest treatment effect was observed in the question related to the impact of HF on the patient's enjoyment of life
- An effect on orthopnea suggested a benefit among patients with more severe HF
- The only question where no treatment benefit was observed was for "dressing yourself," which requires minimal exertion and was not a limitation for most patients in either treatment arm at baseline or Month 12
- Patients in the placebo group showed higher rates of worsening for almost all KCCQ questions compared with patisiran (data not shown)

HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary.

Treatment Effects across Individual Questions in the KCCQ-OS (cont'd)

Figure 4. Mean Treatment Difference in Change from Baseline to Month 12 in Individual KCCQ-OS Questions



KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; Q, question.

Conclusions

- In APOLLO-B, patients with ATTR cardiac amyloidosis showed improvements in health status and quality of life in KCCQ Overall Score and across all four of its domains with patisiran compared with placebo at Month 12
- Greater percentages of patisiran- versus placebo-treated patients had KCCQ-OS improvements of ≥+5 ($p<0.05$), ≥+10, and ≥+20 points at Month 12, and a smaller percentage had a decline of ≤−5, ≤−10, and ≤−20 points
- Treatment effects favoring patisiran versus placebo were observed across 19 of 20 questions that assess the impact of heart failure on symptoms, physical and social limitations, and quality of life, with the largest effects being observed on enjoyment of life, severity of shortness of breath and fatigue, and activities requiring greater exertion

ATTR, transthyretin-mediated; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary.

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Conflict	Disclosures
Alnylam Pharmaceuticals	Consulting fees

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