Effect of Patisiran Treatment in Patients with hATTR Amyloidosis with Cardiomyopathy and Polyneuropathy: Post-hoc Analysis of the APOLLO-B Study

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Background and Rationale

Transthyretin-mediated (ATTR) Amyloidosis

- Cardiomyopathy is a frequent manifestation in patients with wild-type ATTR (ATTRwt) or hereditary ATTR (hATTR, also known as ATTRv) amyloidosis[1–5]
- The majority of individuals with hATTR amyloidosis develop a mixed phenotype of cardiomyopathy and polyneuropathy[6,7]

Patisiran

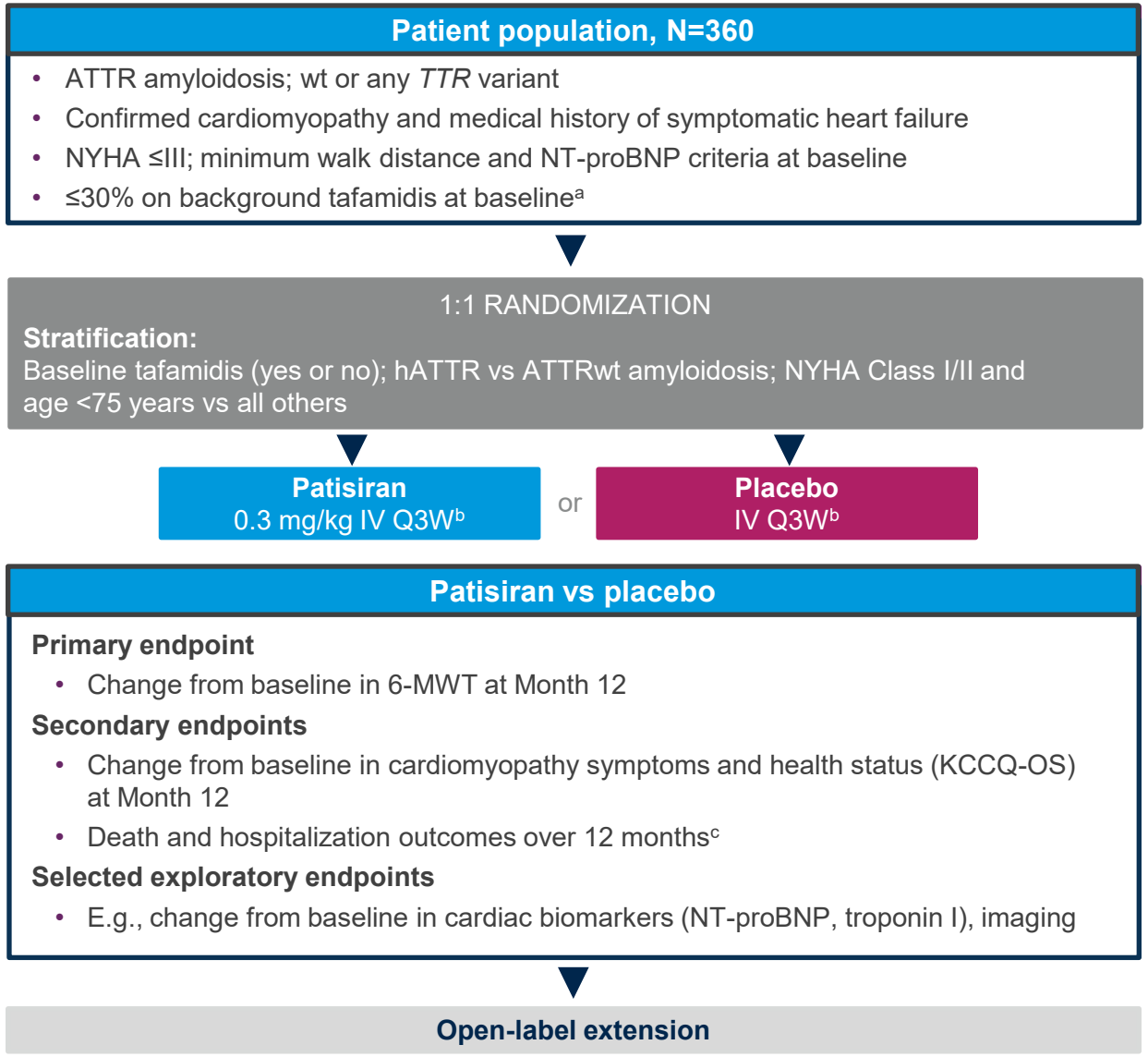
- IV-administered RNAi therapeutic approved for the treatment of hATTR amyloidosis with polyneuropathy
- Prior clinical data in patients with hATTR amyloidosis with polyneuropathy suggest the potential for patisiran to also improve cardiac manifestations in this population[7,8]

Phase 3 APOLLO-B Study

- Randomized, double-blind, placebo-controlled study in patients with ATTR amyloidosis with cardiomyopathy
- APOLLO-B demonstrated the clinical efficacy of patisiran treatment (vs placebo) in patients with ATTR amyloidosis with cardiomyopathy[9–11]

Objective of the Current Study

- To conduct additional, post-hoc analyses assessing the clinical efficacy of patisiran in a subgroup of patients with hATTR amyloidosis with cardiomyopathy and polyneuropathy (mixed phenotype)



[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 received following pre-medications or equivalent at least 60 min. before each study drug infusion: dexamethasone; oral acetaminophen; H1 and H2 blockers. [c]Included composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at basline; and composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in overall population. **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin-mediated CV, cardiovascular; hATTR, hereditary transthyretin-mediated; HF, heart failure; IV, intravenous; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; Q3W, once every 3 weeks; RNAi, ribonucleic acid interference; TTR, transthyretin; wt, wild-type. 1. Castano et al. *Heart Fail Rev* 2015;20:163–78; 2. Swiecicki et al. *Amyloid* 2015;22:123–31; 3. Ruberg et al. *Am Heart J* 2012;164:222–8.e1; 4. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 5. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 6. Rapezzi C 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. Maurer et al. *ISA congress* 2022. Presentation; 10. Maurer et al. *HFSA congress* 2022. Poster; 11. Kale et al. *HFSA congress* 2022. Poster.

Baseline Characteristics of Patients with Mixed Phenotype

Mixed phenotype subgroup criteria[a]

hATTR amyloidosis and at least one of the following:

- A history of polyneuropathy
- PND score ≥I
- Norfolk QOL-DN score ≥30
- Plasma NfL > upper limit of age-partitioned reference values identified by Mayo Clinic laboratories[b,c]

AND

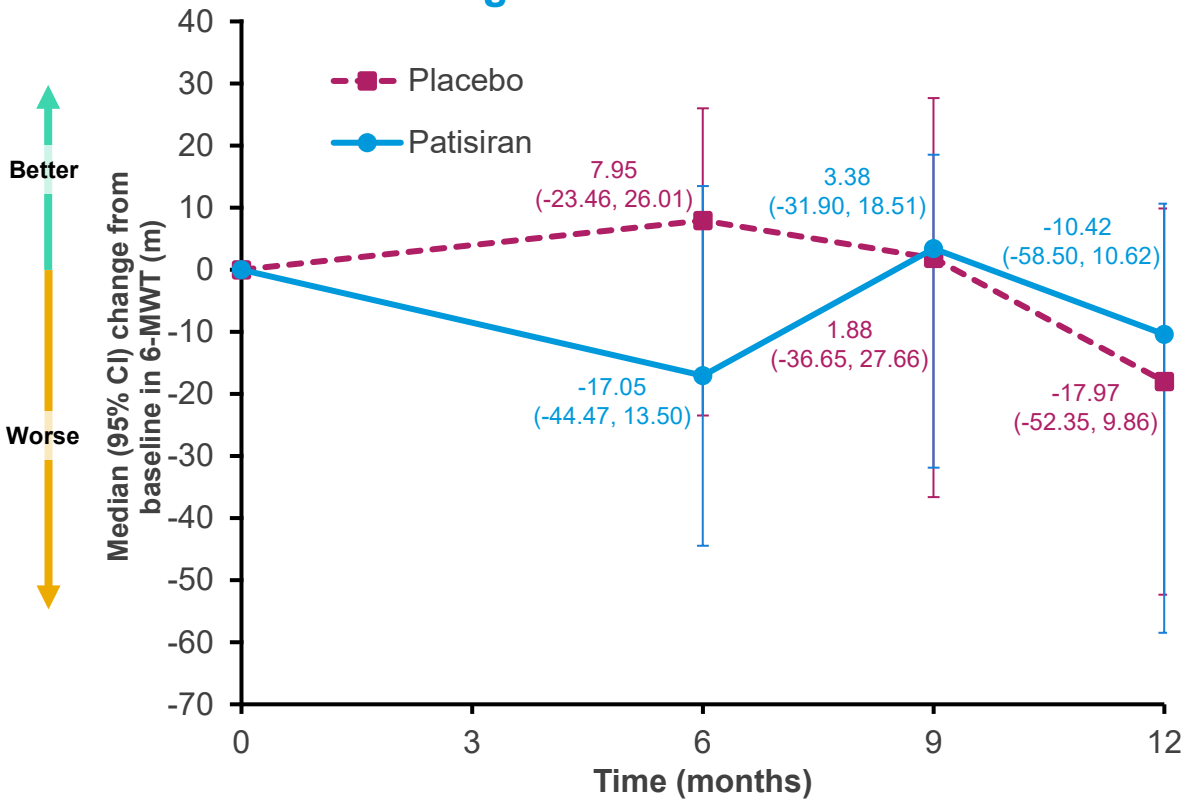
No additional known disease or condition that can cause or contribute to polyneuropathy

Baseline Characteristic	Patisiran (n=31)	Placebo (n=28)
Age (years), median (range)	70 (47–85)	66 (41–85)
Male sex, n (%)	20 (64.5)	21 (75.0)
V122I, n (%)	17 (54.8)	8 (28.6)
Baseline tafamidis use, n (%)	4 (12.9)	4 (14.3)
NYHA Class, n (%)		
Class I	1 (3.2)	4 (14.3)
Class II	29 (93.5)	22 (78.6)
Class III	1 (3.2)	2 (7.1)
Gillmore et al ATTR Amyloidosis Stage, n (%)		
Stage I	20 (64.5)	20 (71.4)
Stage II	8 (25.8)	7 (25.0)
Stage III	3 (9.7)	1 (3.6)
PND score, n (%)		
0	4 (12.9)	7 (25.0)
I	18 (58.1)	17 (60.7)
II	9 (29.0)	4 (14.3)
6-MWT, m, mean (SD)	317.63 (88.89)	370.58 (103.83)
KCCQ-OS, mean (SD)	57.967 (19.799)	67.522 (23.205)
Norfolk QOL-DN, mean (SD)	37.2 (23.5)	26.6 (28.4)
NT-proBNP, ng/L, mean (SD)	2492.4 (2051.6)	2303.7 (1954.6)
NfL, pg/mL, mean (SD)[d]	90.2 (50.3)	55.0 (25.7)

[a]Mixed phenotype subgroup criteria were defined at baseline. [b]Reference values were established by Mayo Clinic laboratories based on https://www.mayocliniclabs.com/test-catalog/overview/616854#Clinical-and-Interpretive (Accessed March 21, 2023). [c]Bornhorst et al. *Clinica Chimica Acta* 2022;535:153–6. [d]n=9 (patisiran), n=12 (placebo). **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; hATTR, hereditary transthyretin-mediated; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NfL, neurofilament light chain; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; QOL-DN, quality of life-diabetic neuropathy; SD, standard deviation.

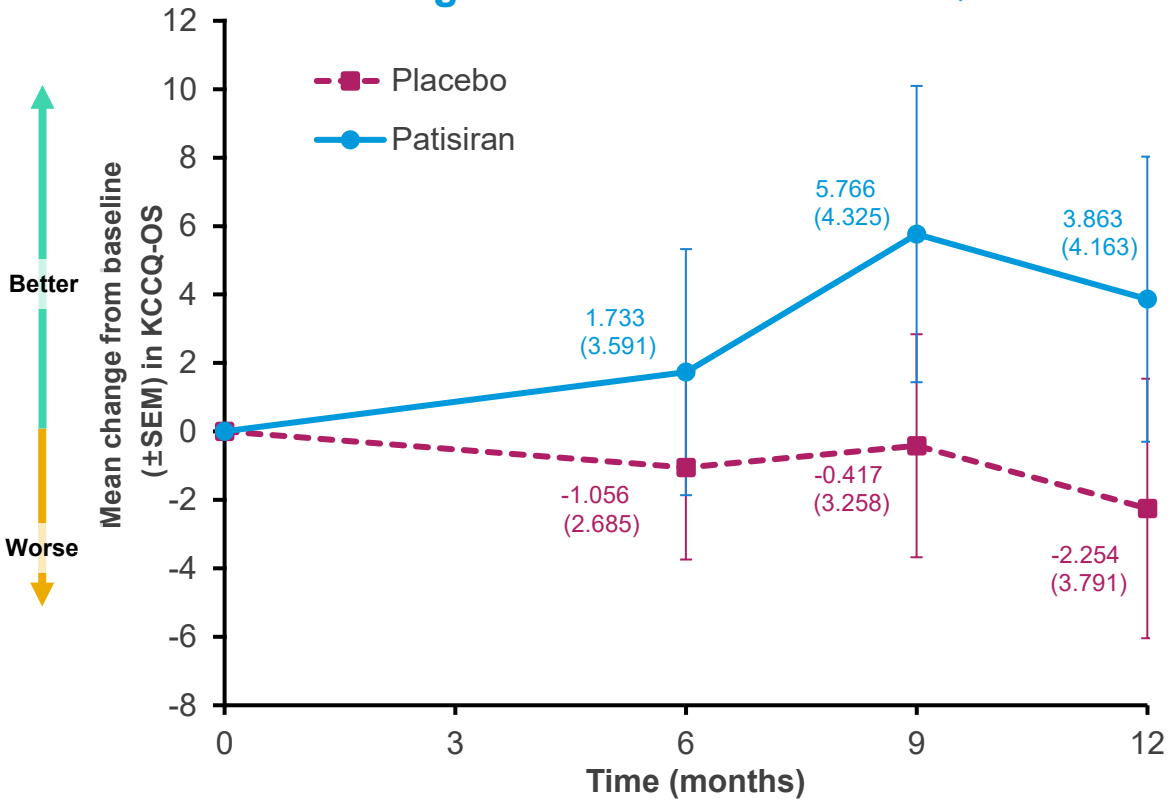
Change in Functional Capacity (6-MWT), Health Status, and Quality of Life (KCCQ-OS) with Patisiran and Placebo in the Mixed Phenotype Group[a]

Change from Baseline in 6-MWT



N evaluable				
Placebo	28	28	28	28
Patisiran	31	31	31	31

Change from Baseline in KCCQ-OS

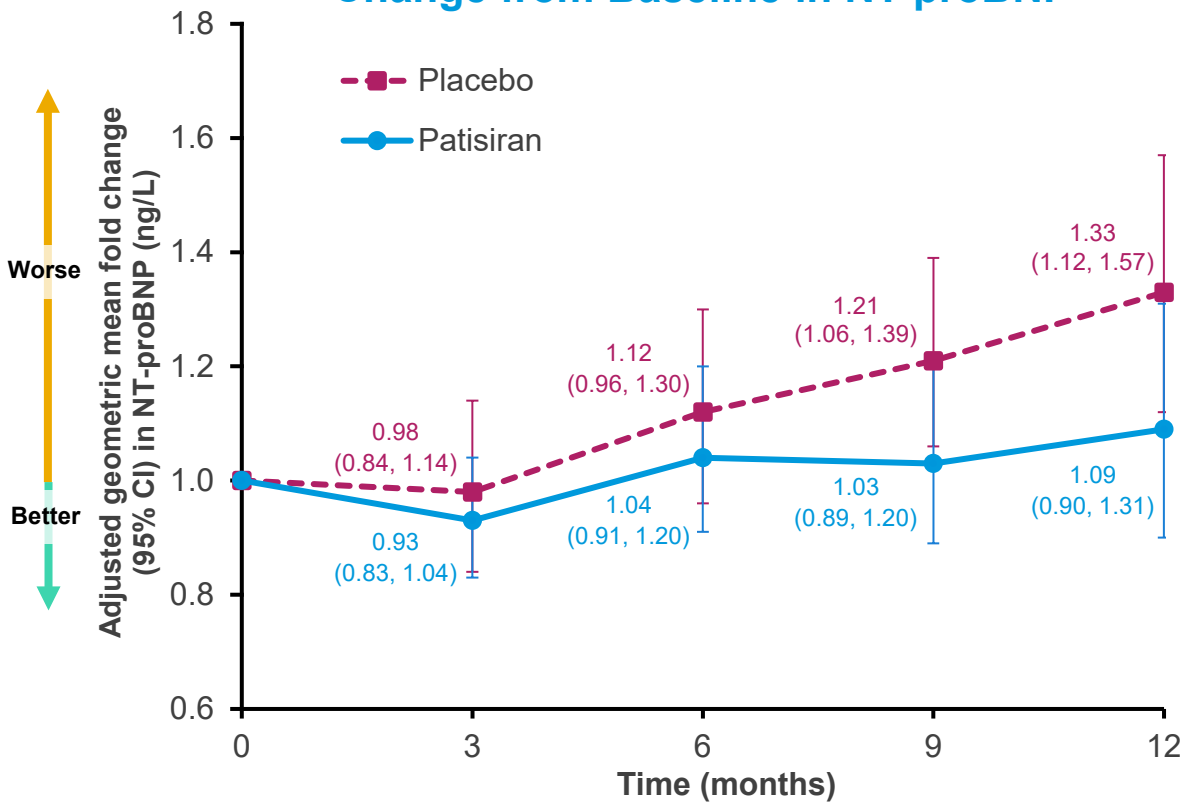


N evaluable				
Placebo	28	27	27	26
Patisiran	31	31	29	30

Baseline median (range) 6-MWT values for mixed phenotype subgroup: Placebo, 379.53 (151.3–539.1); Patisiran, 318.35 (155.7–491.8); for total APOLLO-B population: Placebo, 367.74 (130.0–740.0); Patisiran, 358.00 (155.7–808.0). Baseline mean (SD) KCCQ-OS values for mixed phenotype subgroup: Placebo, 67.522 (23.205); Patisiran, 57.967 (19.799). Baseline mean (SD) KCCQ-OS values for the total APOLLO-B population: Placebo, 70.330 (20.709); Patisiran, 69.836 (21.178). [a]This post-hoc analysis was descriptive only and did not include statistical hypothesis testing. The mixed phenotype subgroup size was not powered to make confirmative statements with these endpoints. **Abbreviations:** 6-MWT, 6-minute walk test; CI, confidence interval; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; QOL, quality of life; SD, standard deviation; SEM, standard error of the mean.

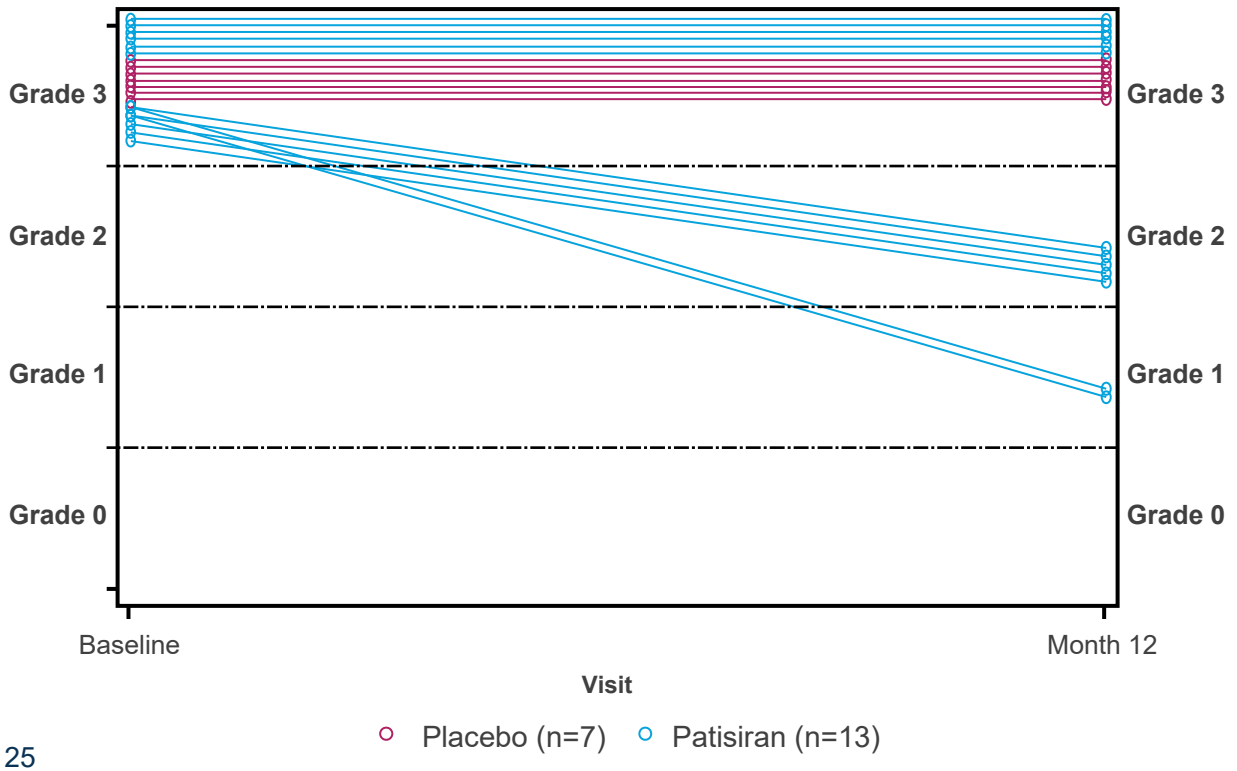
Change in NT-proBNP and Perugini Grade with Patisiran and Placebo in the Mixed Phenotype Group[a]

Change from Baseline in NT-proBNP



N evaluable					
Placebo	28	27	28	27	25
Patisiran	31	31	31	28	30

Change from Baseline in Perugini Grade in Evaluable Patients



Baseline median (IQR) NT-proBNP (ng/L) values for mixed phenotype subgroup: Placebo, 2095.5 (679.0–3125.0); Patisiran, 1991.0 (918.0–2921.0); for the total APOLLO-B population: Placebo, 1813 (952–3079); Patisiran, 2008 (1135–2921). [a]This post-hoc analysis was descriptive only and did not include statistical hypothesis testing. The mixed phenotype subgroup size was not powered to make confirmative statements with these endpoints.

Abbreviations: CI, confidence interval; IQR, interquartile range; NT-proBNP, *N*-terminal pro-brain natriuretic peptide.

Summary

- At Month 12, patisiran showed a directional trend compared with placebo toward benefit in functional capacity (6-MWT), health status, and quality of life (KCCQ-OS) in patients with hATTR amyloidosis with a mixed phenotype
  - The results of these patients are generally consistent with those of the overall population in the APOLLO-B study

- The effect of patisiran on NT-proBNP compared with placebo in patients with hATTR amyloidosis with a mixed phenotype was consistent with that observed in the overall APOLLO-B population

- In a cohort of patients undergoing technetium scintigraphy, reductions in Perugini grade were noted in patients receiving patisiran but not in those receiving placebo

- Overall, this post-hoc analysis showed consistent results with the overall APOLLO-B population, demonstrating a trend toward benefit of patisiran vs placebo in patients with hATTR amyloidosis with a mixed phenotype

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6-MWT, 6-minute walk test; hATTR, hereditary transthyretin-mediated; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; TTR, transthyretin.