Patisiran Treatment for ATTR Cardiac Amyloidosis: 18-Month Results of the Phase 3 APOLLO-B Study

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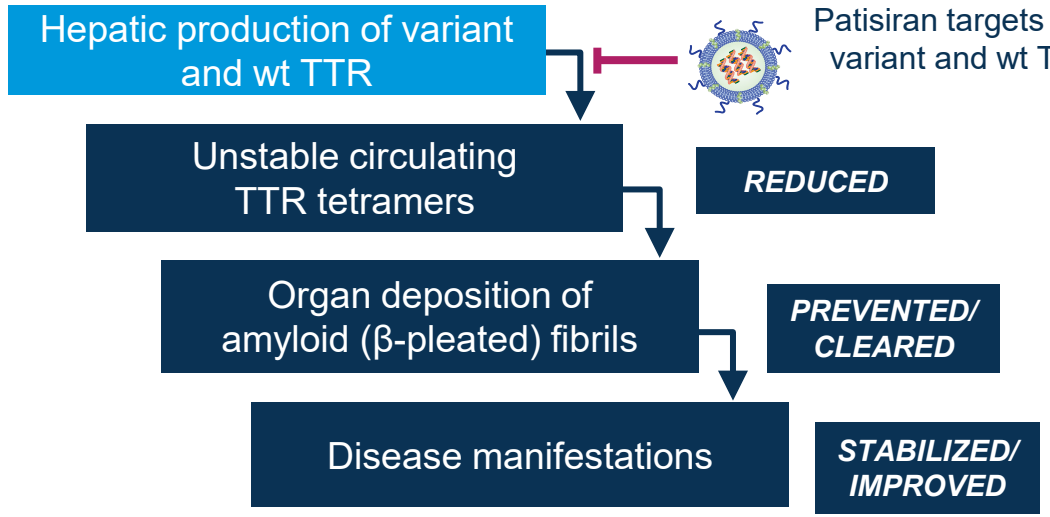
20th – 23rd May 2023 || Annual Meeting of the European Society of Cardiology: Heart Failure 2023

Introduction

Transthyretin (ATTR) Amyloidosis

- A progressive and fatal disease caused by accumulation of amyloid fibrils in multiple organs[1–4]
- Ongoing TTR amyloid deposition in the heart drives the progression of cardiomyopathy, leading to[5–11]:
  - Worsening HF and arrhythmias
  - Decline in functional status and QOL

Therapeutic Hypothesis



Patisiran

- IV-administered RNAi therapeutic approved for the treatment of ATTRv amyloidosis with polyneuropathy
- Prior clinical data in patients with ATTRv amyloidosis with polyneuropathy suggest the potential for patisiran to improve cardiac manifestations of ATTR amyloidosis[11,12]

APOLLO-B Phase 3 Study in ATTR Cardiac Amyloidosis

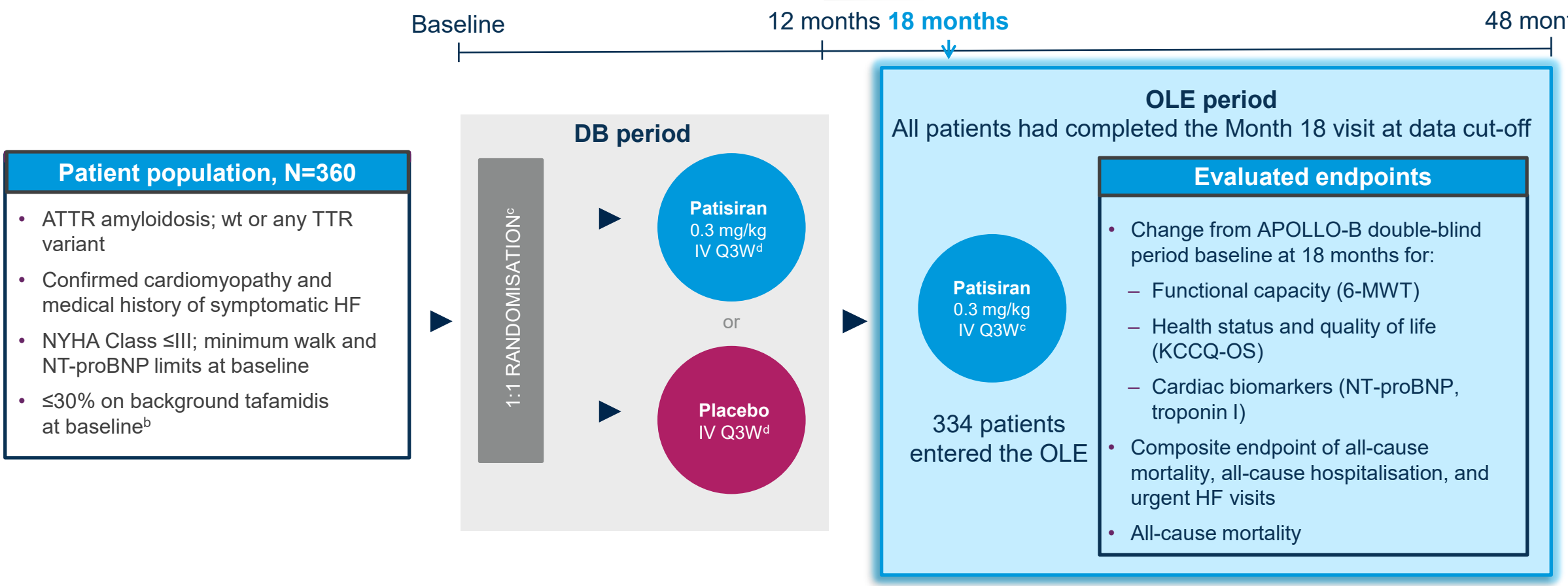
- During the 12-month (M), double-blind (DB) period of the Phase 3 APOLLO-B study (NCT03997383), patisiran preserved functional capacity, health status and QOL in patients with ATTR cardiac amyloidosis whereas placebo was associated with steady worsening[13]
  - Patients completing the 12M DB period were eligible for up to 36M participation in the open-label extension (OLE) where all patients received patisiran

Abbreviations: ATTR amyloidosis, transthyretin amyloidosis; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; DB, double-blind; HF, heart failure; IV, intravenous; OLE, open-label extension; QOL, quality of life; RNAi, ribonucleic acid interference; TTR, transthyretin; wt, wild-type. **References:** 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. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 5. Castano et al. *Heart Fail Rev* 2015;20:163–78; 6. Swiecicki et al. *Amyloid* 2015;22:123–31; 7. Ruberg et al. *Am Heart J* 2012;164:222–8.e1; 8. Sattianayagam et al. *Eur Heart J* 2012;33:1120–7; 9. Gertz et al. *Mayo Clin Proc* 1992;67:428–40; 10. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 11. Adams et al. *N Engl J Med* 2018;379:11–21; 12. Solomon et al. *Circulation* 2019;139:431–43; 13. Maurer et al. *HFSA Congress* 2022. Poster Presentation

Methods

APOLLO-B Study Design in Patients with ATTR Cardiac Amyloidosis

- 360 patients enrolled in APOLLO-B at 69 sites in 21 countries
- 334 patients entered the OLE period; here we present results from an 18-month interim analysis[a]



[a]Data from the timepoint after which all active patients had completed at least their Month 18 visit (19 December 2022). [b]Where tafamidis is available as local standard of care; receiving tafamidis treatment ≥6 months with disease progression in opinion of investigator. [c]Stratification: Baseline tafamidis (yes or no); ATTRv vs ATTRwt amyloidosis; NYHA Class I/II and age <75 years vs all others. [d]To reduce likelihood of infusion-related reactions, patients receive the following premedications or equivalent at least 60 minutes before each study drug infusion: dexamethasone; oral acetaminophen; H1 and H2 blockers. **Abbreviations:** 6-MWT, 6-minute walk test; ATTR amyloidosis, transthyretin amyloidosis; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; DB, double-blind; HF, heart failure; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; Q3W, once every 3 weeks; TTR, transthyretin; wt, wild-type.

Baseline Demographics and Disease Characteristics

- Baseline demographics and disease characteristics were comparable across the treatment groups

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)	140 (79)
Asian	23 (13)	15 (8)
Black or African American	16 (9)	15 (8)
ATTRwt amyloidosis, n (%)	144 (80)	144 (81)
Time since diagnosis of ATTR amyloidosis, median (range), years	0.8 (0–6)	0.4 (0–10)
Baseline tafamidis use, n (%)	46 (25)	45 (25)
NYHA class, n (%)		
Class I	10 (6)	15 (8)
Class II	156 (86)	150 (84)
Class III	15 (8)	13 (7)

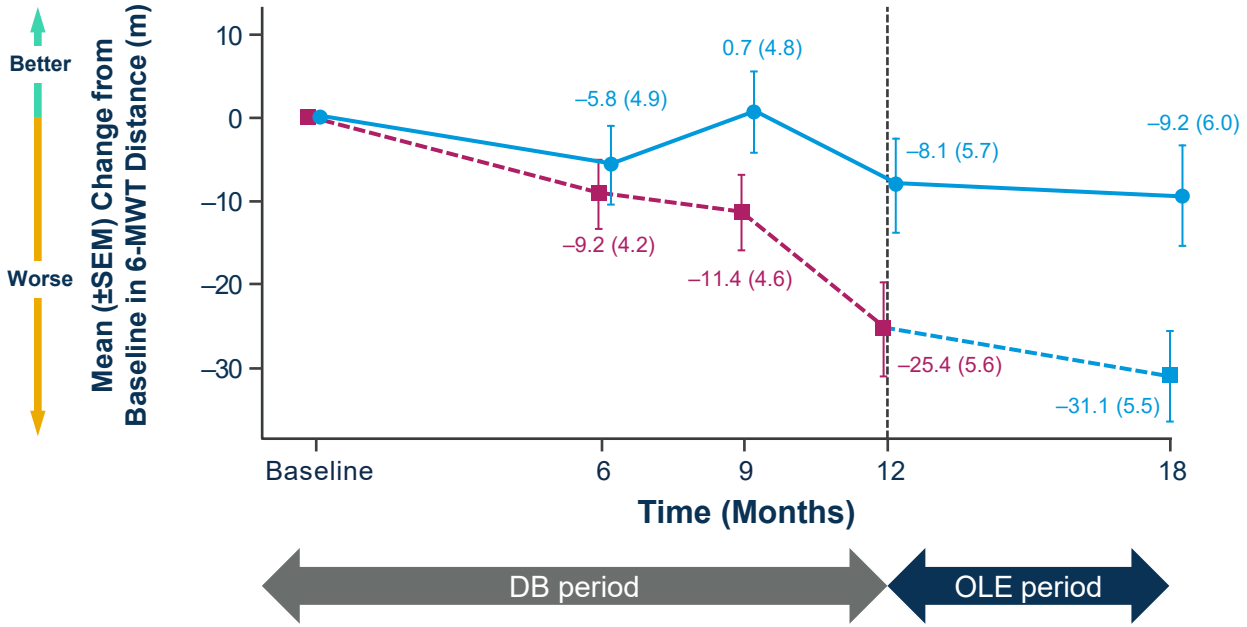
Characteristic	Patisiran (N=181)	Placebo (N=178)
ATTR amyloidosis stage[a], n (%)		
Stage 1	124 (69)	120 (67)
Stage 2	46 (25)	45 (25)
Stage 3	11 (6)	13 (7)
PND score, n (%)		
0: no impairment	96 (53)	109 (61)
I: preserved walking, with sensory disturbances	63 (35)	55 (31)
II: impaired walking without need for a stick or crutches	22 (12)	14 (8)
6-MWT, 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. **Abbreviations:** 6-MWT, 6-minute walk test; ATTR amyloidosis, transthyretin amyloidosis; 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; PND, polyneuropathy disability; SD, standard deviation.

Change from Baseline in Functional Capacity (6-MWT) and Health Status and QOL (KCCQ-OS) over 18 Months

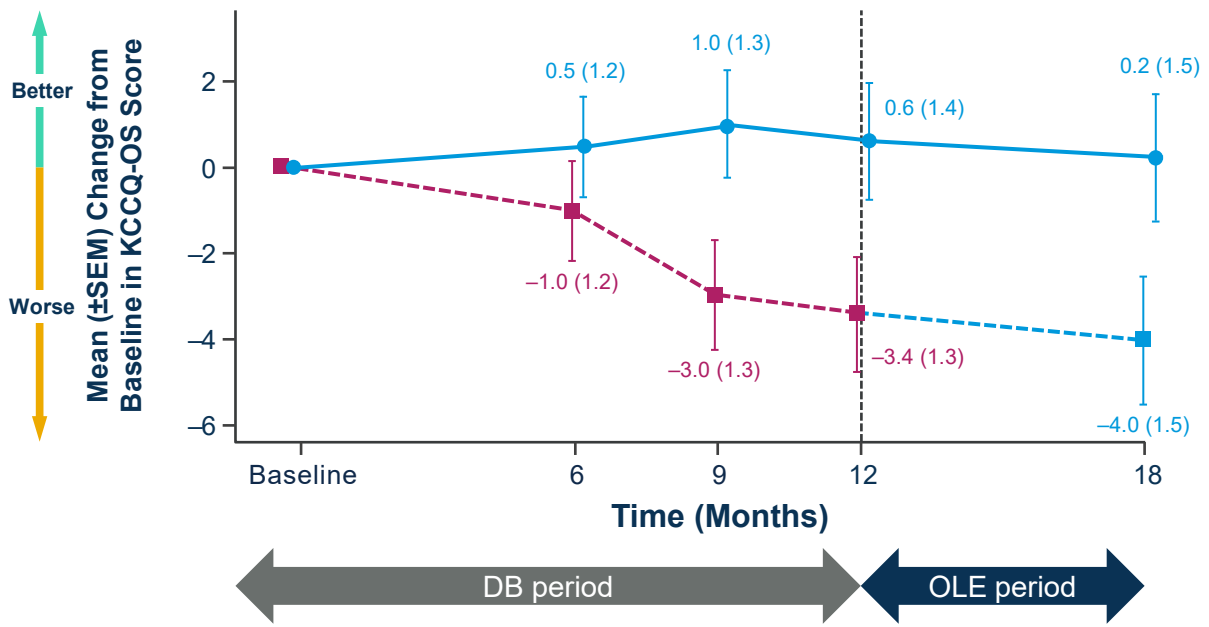
- Preservation of functional capacity and health status and QOL was sustained through 18 months of treatment in patients receiving patisiran in both DB and OLE periods
- In patients receiving placebo in the DB period, initiation of patisiran in the OLE was associated with a slower rate of worsening (6-MWT) or relative stability (KCCQ-OS) at Month 18 compared with the DB period

Mean Change from Baseline in 6-MWT[a,b,c]



No. of patients					
Placebo	178	165	165	164	146
Patisiran	181	162	167	167	149

Mean Change from Baseline in KCCQ-OS[c,d]



No. of patients					
Placebo	178	171	168	167	155
Patisiran	181	170	171	171	157

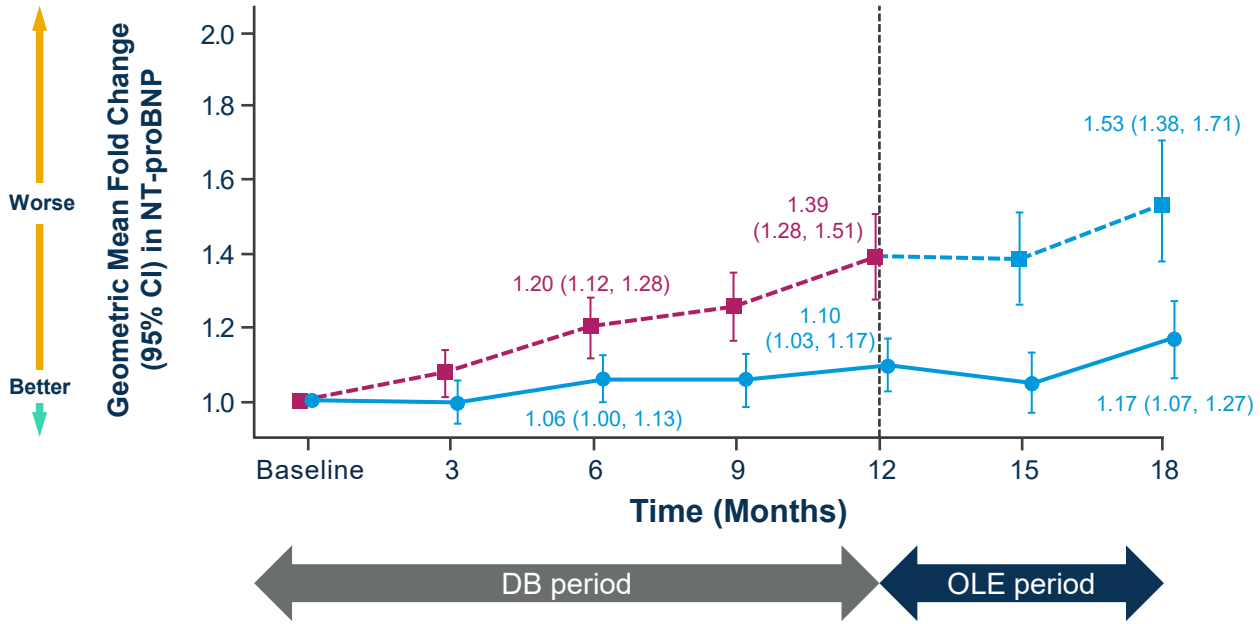
Patisiran Placebo

[a]Baseline is defined as the last non-missing value available prior to first dose of study drug in the DB period. All patients received patisiran after Month 12. [b]Assessments where the timer was stopped after ≤4 minutes or conducted using unapproved walking aid are excluded from the analysis. [c]Visits with complete data collection are presented. [d]Baseline is defined as the last non-missing value available on or before the date of first dose of study drug in the DB period. All patients received patisiran after Month 12. **Abbreviations:** 6-MWT, 6-minute walk test; DB, double-blind; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; OLE, open-label extension; QOL, quality of life; SEM, standard error of the mean.

Change from Baseline in Cardiac Biomarkers (NT-proBNP, Troponin I)

- Patients originally randomised to patisiran maintained relatively stable NT-proBNP and troponin I levels from baseline to Month 18
- Patients randomised to placebo showed steadily rising rates of cardiac biomarker levels up to Month 12, which then slowed or stabilised after initiation of patisiran

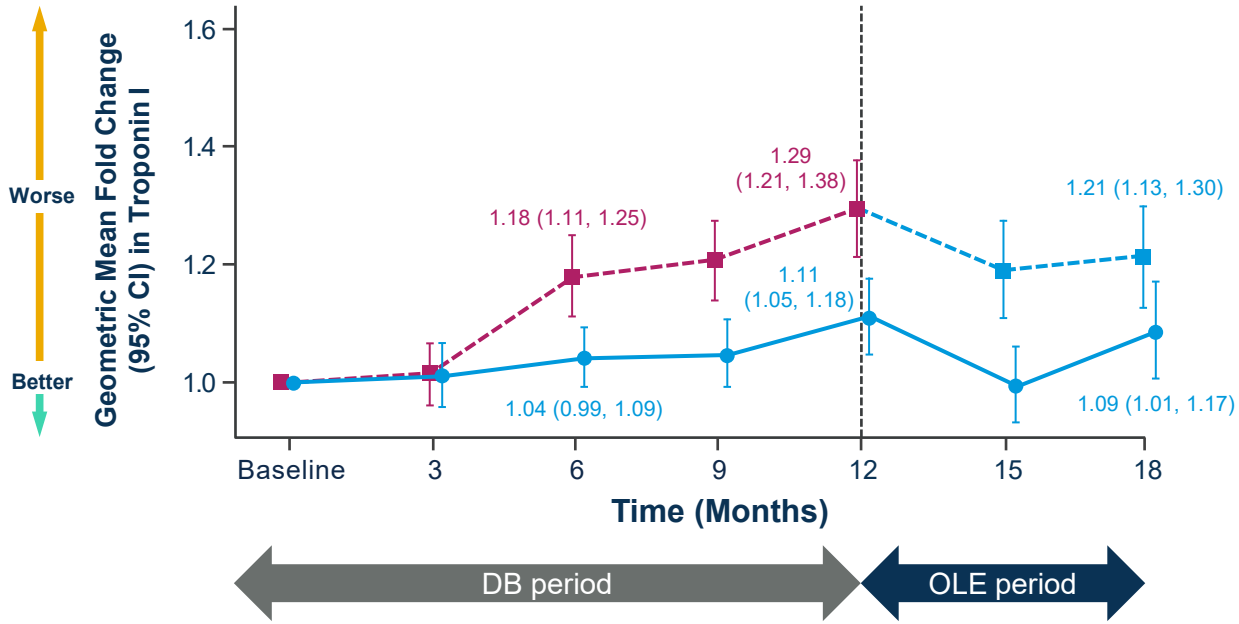
Geometric Mean Fold Change from Baseline in NT-proBNP[a]



No. of patients

Placebo	178	168	165	164	163	156	152
Patisiran	181	171	169	169	167	157	157

Geometric Mean Fold Change from Baseline in Troponin I[a]



No. of patients

Placebo	172	158	162	156	155	150	145
Patisiran	174	161	162	160	158	146	147

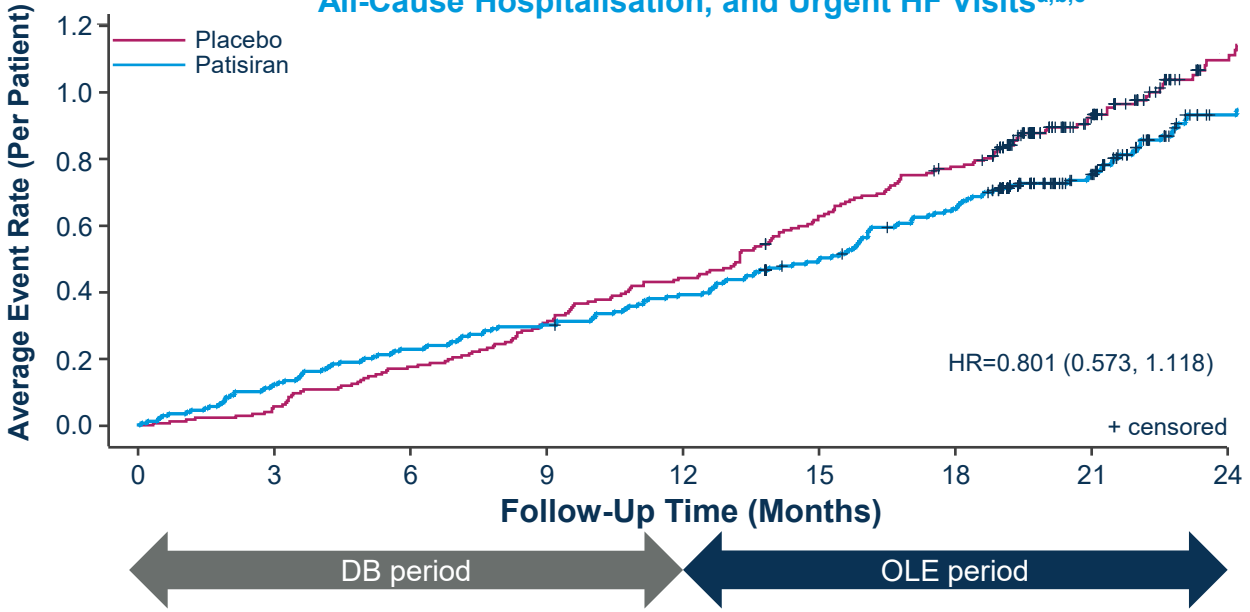
Patisiran Placebo

[a]Visits with complete data collection are presented. Baseline is defined as the last non-missing value available on or before the date of first dose of study drug in the DB period. All patients received patisiran after Month 12. **Abbreviations:** CI, confidence interval; DB, double-blind; NT-proBNP, *N*-terminal prohormone of B-type natriuretic peptide; OLE, open-label extension.

Composite Endpoints

- The study was not long enough nor powered to show treatment difference in death and hospitalisation; no statistically significant difference was observed
- During the study (DB + OLE periods):
  - The point estimate of HR for the composite of all-cause mortality and frequency of all-cause hospitalisation and urgent HF visits was 0.801 (95% CI, 0.573–1.118)
  - The HR for all-cause mortality was 0.554 (95% CI, 0.281–1.094). The number of events in the all-cause mortality efficacy analysis was 13 (7.2%) in patients randomized to patisiran and 23 (12.9%) in patients randomized to placebo

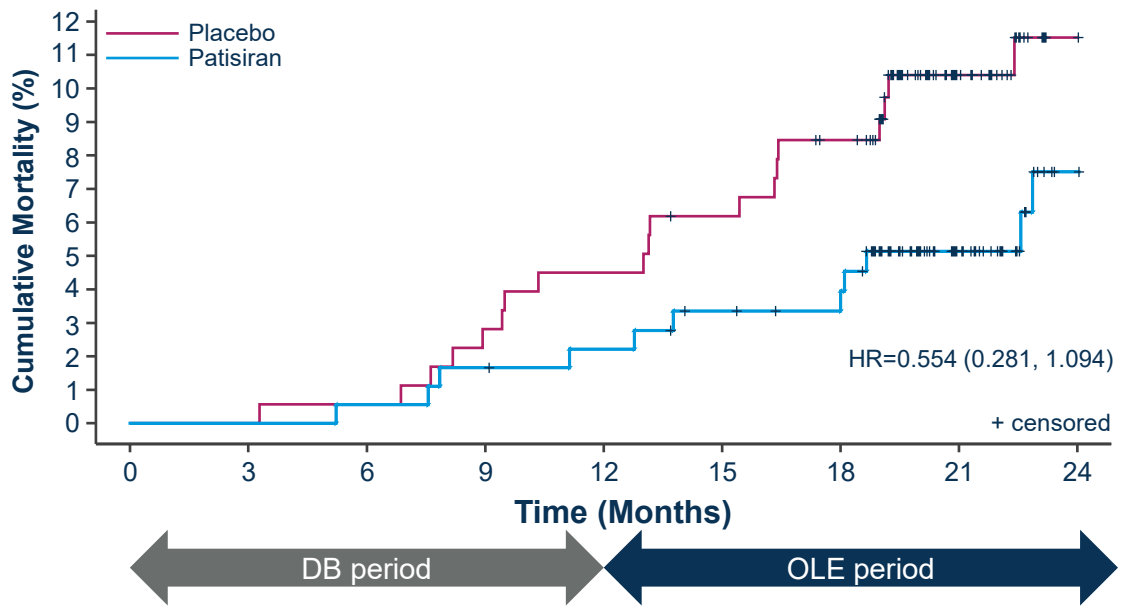
Mean Cumulative Function Plot of All-Cause Mortality, All-Cause Hospitalisation, and Urgent HF Visits[a,b,c]



No. of patients

Placebo	178	178	177	174	170	165	159	103	66
Patisiran	181	181	180	178	176	165	163	108	71

Cumulative Plot of All-Cause Death[a,b,d,e]



No. of patients

Placebo	178	178	177	173	170	165	159	96	66
Patisiran	181	181	180	178	176	165	163	105	71

[a]Heart transplantation and left ventricular assist device placement are handled in the same manner as death. Deaths, hospitalisations, and urgent HF visits due to COVID-19 are excluded from analysis. For patients who discontinued treatment during the DB period, events occurring after Day 417 are excluded. For patients who discontinued treatment during the OLE period, events occurring more than 90 days after last patisiran dose are excluded. The figure is truncated at Day 731; events that occurred after Day 731 are included in the estimate of the HR but not shown in the figure. [b]The analysis was based on the ITT principle and analysed each treatment arm from initial randomisation through the cut-off date, ignoring entry into the OLE. [c]The HR is derived using the modified Andersen–Gill model stratified by baseline tafamidis use, including randomised treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates. An HR <1 represents a favourable outcome for patisiran. [d]The HR is derived using the Cox proportional hazards model including randomised treatment as a covariate. [e]4 and 2 deaths in patients initially randomised to placebo and patisiran, respectively, that occurred after Day 731 are included in the estimate of HR but not shown in the figure.
Abbreviations: ATTR amyloidosis, transthyretin amyloidosis; DB, double-blind; CI, confidence interval; HF, heart failure; HR, hazard ratio; ITT, intent-to-treat; NYHA, New York Heart Association; OLE, open-label extension.

Patisiran Demonstrated an Acceptable Safety Profile

- Median exposure was 9.6 months (range 0.7–24.6 months) in the placebo/patisiran group and 21.8 months (range 0.0–37.0 months) in the patisiran/patisiran group
- The majority of AEs were mild or moderate in severity
- The most common related AE was infusion-related reactions (14.1% of patients)
- The safety profile of patisiran was consistent with previous findings with no new safety concerns identified

Summary of Safety in Patients Receiving Patisiran[a]

At Least 1 Event	Placebo/Patisiran N=166 (PY=149.6)		Patisiran/Patisiran N=181 (PY=332.4)		All Patisiran N=347 (PY=482.0)	
	N (%)	ER	N (%)	ER	N (%)	ER
AEs	156 (94.0)	784.6	174 (96.1)	613.8	330 (95.1)	666.8
Serious AEs	70 (42.2)	107.6	102 (56.4)	71.3	172 (49.6)	82.6
Severe AEs	56 (33.7)	76.9	75 (41.4)	53.6	131 (37.8)	60.8
AEs leading to study drug discontinuation	9 (5.4)	6.7	11 (6.1)	4.2	20 (5.8)	5.0
Deaths[b]	8 (4.8)	5.3	12 (6.6)	3.6	20 (5.8)	4.1

[a]Cumulative safety data during patisiran treatment as of a data cut-off date of 19 December 2022. Note: The placebo/patisiran group does not include safety events during treatment with placebo from the double-blind period
[b]Includes all AEs with an outcome of fatal (including COVID-19) regardless of treatment-emergent classification but does not include deaths that occurred after study withdrawal. Heart transplant and LVAD were not included or counted as fatal events in the safety analysis population.
Abbreviations: AE, adverse event; ER, exposure-adjusted event rate per 100 patient-years; PY, patient-years.

Cardiac Safety

- The type and nature of cardiac events observed were consistent with the underlying disease and with those reported during the DB period

Category	DB/OLE on Patisiran					
	Placebo/Patisiran (N=166, PY=149.6)		Patisiran/Patisiran (N=181, PY=332.4)		All Patisiran (N=347, PY=482.0)	
	N (%)	ER	N (%)	ER	N (%)	ER
Cardiac AEs (Cardiac disorders SOC)	80 (48.2)	94.2	102 (56.4)	87.0	182 (52.4)	89.2
Cardiac SAEs (Cardiac disorders SOC)	39 (23.5)	35.4	54 (29.8)	25.9	93 (26.8)	28.8
Cardiac arrhythmias (HLGT)	33 (19.9)	32.7	57 (31.5)	34.6	90 (25.9)	34.0
Supraventricular arrhythmias (HLT)	24 (14.5)	22.7	40 (22.1)	24.7	64 (18.4)	24.1
Ventricular arrhythmias and cardiac arrest (HLT)	6 (3.6)	5.3	13 (7.2)	4.8	19 (5.5)	5.0
Cardiac conduction disorders (HLT)	4 (2.4)	2.7	8 (4.4)	2.7	12 (3.5)	2.7
Atrioventricular block complete	3 (1.8)	2.0	2 (1.1)	0.6	5 (1.4)	1.0
Rate and rhythm disorders (HLT)	3 (1.8)	2.0	7 (3.9)	2.4	10 (2.9)	2.3
Cardiac failure SMQ (Broad and narrow)	55 (33.1)	59.5	84 (46.4)	53.0	139 (40.1)	55.0

Cumulative safety data during patisiran treatment as of a data cut-off date of 19 December 2022. Note: The placebo/patisiran group does not include safety events during treatment with placebo from the double-blind period
Abbreviations: AE, adverse event; DB, double-blind; ER, exposure-adjusted event rate per 100 patient-years; HLGT, high-level group term; HLT, high-level term; MedDRA, Medical Dictionaries for Regulatory Activities; OLE, open-label extension; PY, patient-years; SAE, serious adverse event; SMQ, standardized MedDRA Query; SOC, system organ class.

Summary

- Continued treatment with patisiran through 18 months in the OLE period demonstrated evidence of sustained benefit across endpoints
  - Continued stability was observed for 6-MWT and KCCQ-OS, as well as for the cardiac biomarkers NT-proBNP and troponin I
- Placebo-treated patients who initiated patisiran in the OLE appear to show slowing of disease progression or stabilisation across multiple endpoints (6-MWT, KCCQ-OS, NT-proBNP, and troponin I)
- Placebo crossover patients did not recover the functional capacity or health status and QOL that were lost during the DB period relative to those in the patisiran group, highlighting the importance of early treatment initiation
- Composite outcome and mortality analyses across the DB+OLE periods did not show significant differences; however, favourable trends were observed
- Patisiran demonstrated an acceptable safety profile
  - AEs were consistent with the underlying disease and the known safety profile of patisiran
  - No new safety concerns, including cardiac events
- The overall benefit–risk profile of patisiran in patients with ATTR cardiac amyloidosis continued to be favourable through Month 18

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the APOLLO-B study, especially considering the challenges of continuing the study during the COVID-19 pandemic. This study was funded by Alnylam Pharmaceuticals. Medical writing assistance was provided by Kristen Brown, PhD, of Adelphi Communications, Macclesfield, UK, and funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice Guidelines. **Abbreviations:** 6-MWT, 6-minute walk test; AE, adverse event; ATTR amyloidosis, transthyretin amyloidosis; DB, double-blind; KCCQ, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; OLE, open-label extension; QOL, quality of life.