Evaluation of Disease Progression in Patients with ATTR Amyloidosis with Cardiomyopathy Following Treatment with Patisiran: Post hoc Analysis of the APOLLO-B Study

Thibaud Damy[1]; Zubair Shah[2]; Brian Drachman[3]; Pedro Schwartzmann[4,5]; Claudio Tinoco Mesquita[6]; Michael Polydefkis[7]; Laura Obici[8]; Patrick Jay[9]; Shaun Bender[9]; Kelley Capocelli[9]; Mazen Hanna[10]

[1]Referral Center for Cardiac Amyloidosis, Hôpital Henri Mondor, Créteil, France; [2]Department of Cardiovascular Medicine, University of Kansas Medical Center, Kansas City, KS; [3]Department of Cardiovascular Medicine, Penn Presbyterian Medical Center, Philadelphia, PA; [4]Unimed Hospital, Ribeirão Preto, São Paulo, Brazil; [5]Advanced Research Centre, CAPED, Ribeirão Preto, São Paulo, Brazil; [6]Hospital Pró-Cardíaco, Nuclear Medicine, Rio de Janeiro, Brazil; [7]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD; [8]Amyloidosis Research & Treatment Center, Fondazione IRCCS Policlinico San Matteo di Pavia, Pavia, Italy; [9]Alnylam Pharmaceuticals, Cambridge, MA; [10]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH

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Background and Rationale

ATTR Amyloidosis

- A progressive and fatal disease caused by accumulation of amyloid fibrils in multiple organs[1–3]
- Ongoing TTR amyloid deposition in the heart drives the progression of CM, leading to:[1–3]
  - Worsening HF and arrhythmias
  - Decline in functional status and QOL[3–6]

Patisiran

- IV-administered RNAi therapeutic approved for the treatment of ATTRv amyloidosis with polyneuropathy[7–9]
- Prior clinical data in patients with ATTRv amyloidosis with polyneuropathy[10] and a subgroup with ATTRv amyloidosis with evidence of cardiac amyloid involvement,[11] suggest the potential for patisiran to improve cardiac manifestations of ATTR amyloidosis

APOLLO-B Phase 3 Study in ATTR Amyloidosis with CM

- During the 12-month, double-blind period of the Phase 3 APOLLO-B study (NCT03997383), patisiran preserved functional capacity, health status, and QOL in patients with ATTR amyloidosis with CM, whereas placebo was associated with steady worsening[12]

ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin-mediated (v for variant); CM, cardiomyopathy; HF, heart failure; IV, intravenous; QOL, quality of life; RNAi, RNA interference; TTR, transthyretin. 1. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–91; 3. Chacko et al. *Eur J Heart Fail* 2022;24:1700–12; 4. Fontana et al. *Circulation* 2015;132:1570–9; 5. Lane et al. *Circulation* 2019;140:16–26; 6. Nativi-Nicolau et al. *ESC Heart Failure* 2021;8:3875–84; 7. Coelho et al. *N Engl J Med* 2013;369:819–29; 8. Alnylam Pharmaceutics Inc. 2023 https://www.alnylam.com/sites/default/files/pdfs/ONPATTRO-Prescribing-Information.pdf; 9. European Medicines Agency 2018 https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf; 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. HFSA Congress 2022. Poster Presentation.

Objective

- To evaluate disease progression in APOLLO-B patients following 12 months of treatment with patisiran vs placebo, based on the ESC expert consensus[13] on monitoring patients with ATTR amyloidosis with CM every 6–12 months, using three domains:
  - Clinical and functional
  - Laboratory biomarker
  - Imaging and ECG

ATTR, transthyretin-mediated; CM, cardiomyopathy; ECG, electrocardiography; ESC, European Society of Cardiology. 13. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23:895–905

Methods

- Post hoc analysis of the Phase 3, double-blind, randomized APOLLO-B study assessing disease progression in patients with ATTRv or ATTRwt amyloidosis with CM after treatment with patisiran 0.3 mg/kg IV Q3W vs placebo IV Q3W for 12 months (**Figure 1**)
- Disease progression at 12 months was based on the ESC expert consensus on monitoring patients with ATTR amyloidosis with CM,[13] using three domains: Clinical and functional, Laboratory biomarker, and Imaging and ECG (**Figures 1 and 2**)

Criteria for Disease Progression

- A patient met the criteria for overall disease progression if they fulfilled ≥1 criterion from each of the three domains at Month 12 (**Figure 2**) or the mortality criterion of death prior to the Month 12 visit

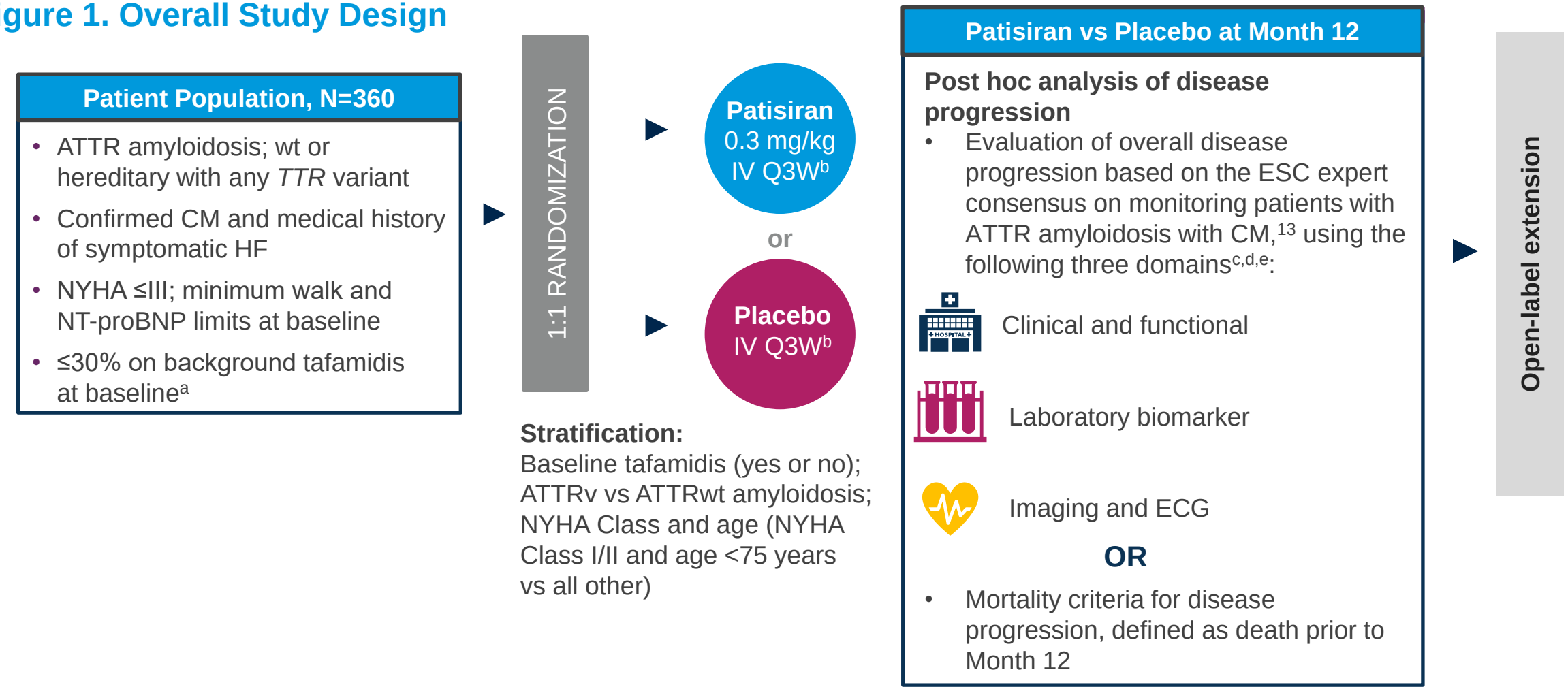
Statistical Analysis

- Patients meeting disease progression criteria are reported descriptively
- A Cochran–Mantel–Haenszel test stratified by baseline tafamidis use was used to obtain ORs with 95% CIs and p-values comparing treatments
- Patients with missing Month 12 data due to COVID-19 were excluded

ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin-mediated (v for variant); ATTRwt, wild-type transthyretin-mediated; CI, confidence interval; CM, cardiomyopathy; ECG, electrocardiography; ESC, European Society of Cardiology; IV, intravenous; OR, odds ratio; Q3W, once every 3 weeks. 13. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23:895–905.

Methods (cont'd)

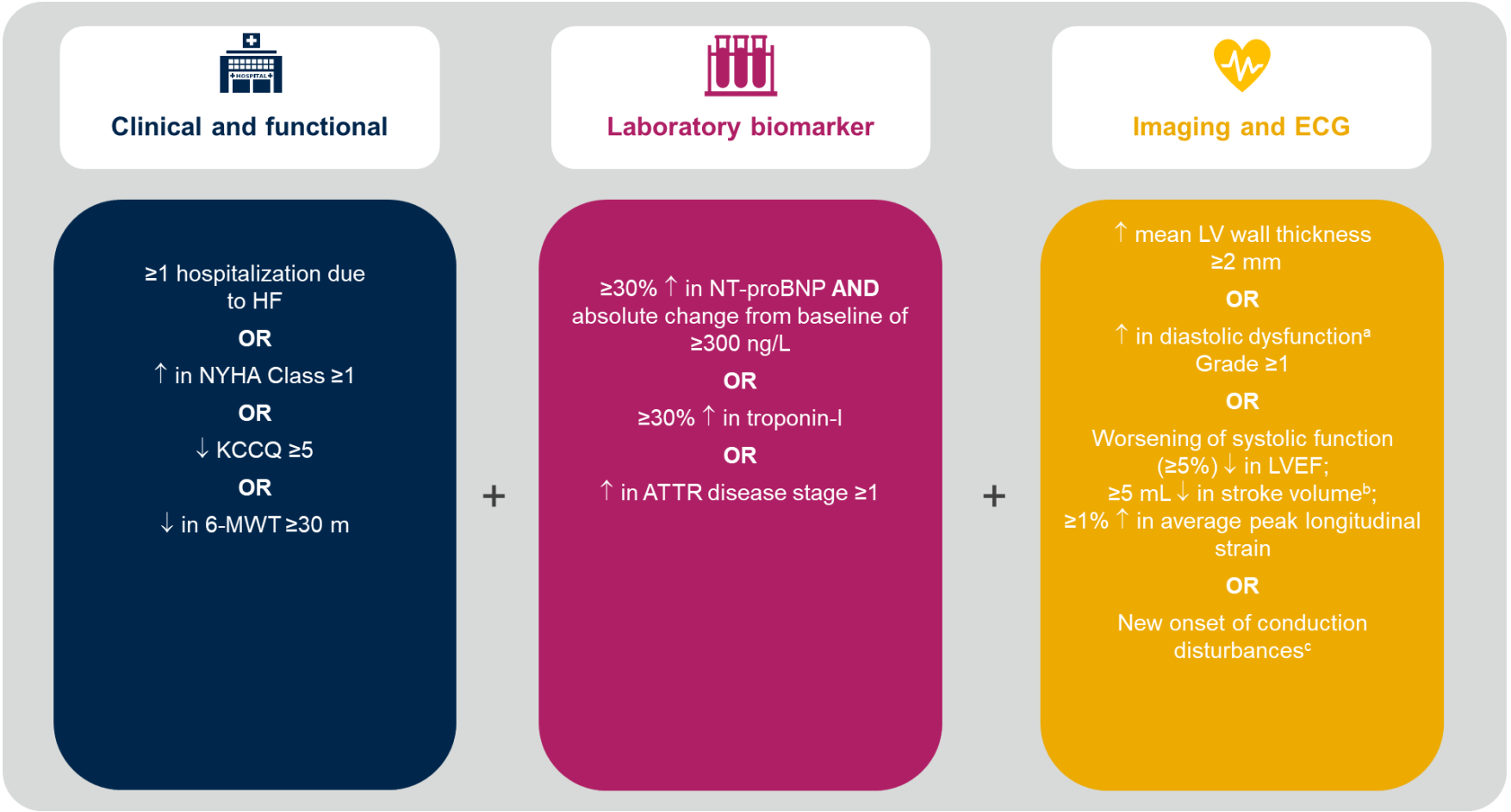
Figure 1. Overall Study Design



[a]Where tafamidis is available as local standard of care; receiving tafamidis treatment for ≥6 months with disease progression in opinion of investigator. [b]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. [c]Disease progression criteria were reported descriptively. A Cochran–Mantel–Haenszel test stratified by baseline tafamidis use was used to obtain ORs with 95% CIs and p-values comparing treatments. [d]Patients missing Month 12 data due to COVID-19 were excluded. [e]Recommended frequency of measurement for 3 domains of ESC criteria was 6-12-month timeframe, whereas this analysis was based on 12 months. ATTR, transthyretin-mediated; ATTRv, hereditary transthyretin-mediated (v for variant); ATTRwt, wild-type transthyretin-mediated; CI, confidence interval; CM, cardiomyopathy; ECG, electrocardiography; ESC, European Society of Cardiology; HF, heart failure; IV, intravenous; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; Q3W, once every 3 weeks; TTR, transthyretin; wt, wild-type. 13. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23:895–905.

Methods (cont'd)

Figure 2. ESC Criteria for Disease Progression at Month 12[13]



[a]Diastolic dysfunction grade defined as 1, if Mitral E/A ratio <0.8; 2, if Mitral E/A ratio ≥0.8 and <2; 3, if Mitral E/A ratio ≥2. [b]Left Ventricular Stroke Volume = Left Ventricular End Diastolic Volume - Left Ventricular End Systolic Volume. [c]Conduction disturbance was defined as an AE with an onset date after randomization and before Month 12 visit with any of the following preferred terms: Cardiac pacemaker insertion; cardiac resynchronization therapy; implantable defibrillator insertion; atrioventricular block; atrioventricular block complete; atrioventricular block first degree; atrioventricular block second degree; bundle branch block left; bundle branch block right; conduction disorder; bradycardia; chronotropic incompetence; sinus arrest; sinus disorder; sinus bradycardia; or sinus node dysfunction. 6-MWT, 6-minute walk test; AE, adverse event; ATTR, transthyretin-mediated; ECG, electrocardiography; ESC, European Society of Cardiology; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association. 13. Garcia-Pavia et al. *Eur J Heart Fail* 2021;23:895–905.

Baseline Demographic and Disease Characteristics

- Baseline demographics and disease characteristics were comparable between the patisiran (n=181) and placebo (n=178) arms (**Table 1**)
- The majority of patients were White (79%) and male (89%) with ATTRwt amyloidosis (80%) and were in ATTR amyloidosis stage I (68%) and NYHA Class II (85%) (**Table 1**)

Table 1. Baseline Characteristics

Characteristic	Patisiran (N=181)	Placebo (N=178)
Age, median (range), years	76 (47–85)	76 (41–85)
Male sex, n (%)	161 (89)	160 (90)
Race, n (%)[a]		
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)
ATTR amyloidosis stage[b], 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)[c]	60.2 (38.2–103.1)[d]
eGFR, mL/min/1.73 m^2, median (IQR)	71.0 (58.0–83.0)	67.0 (51.0–84.0)

[a]Patisiran n=180; placebo n=174. [b]Gillmore staging was used. 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. [c]n=174. [d]n=172. 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; ATTRwt, wild-type transthyretin-mediated; 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 score; SD, standard deviation.

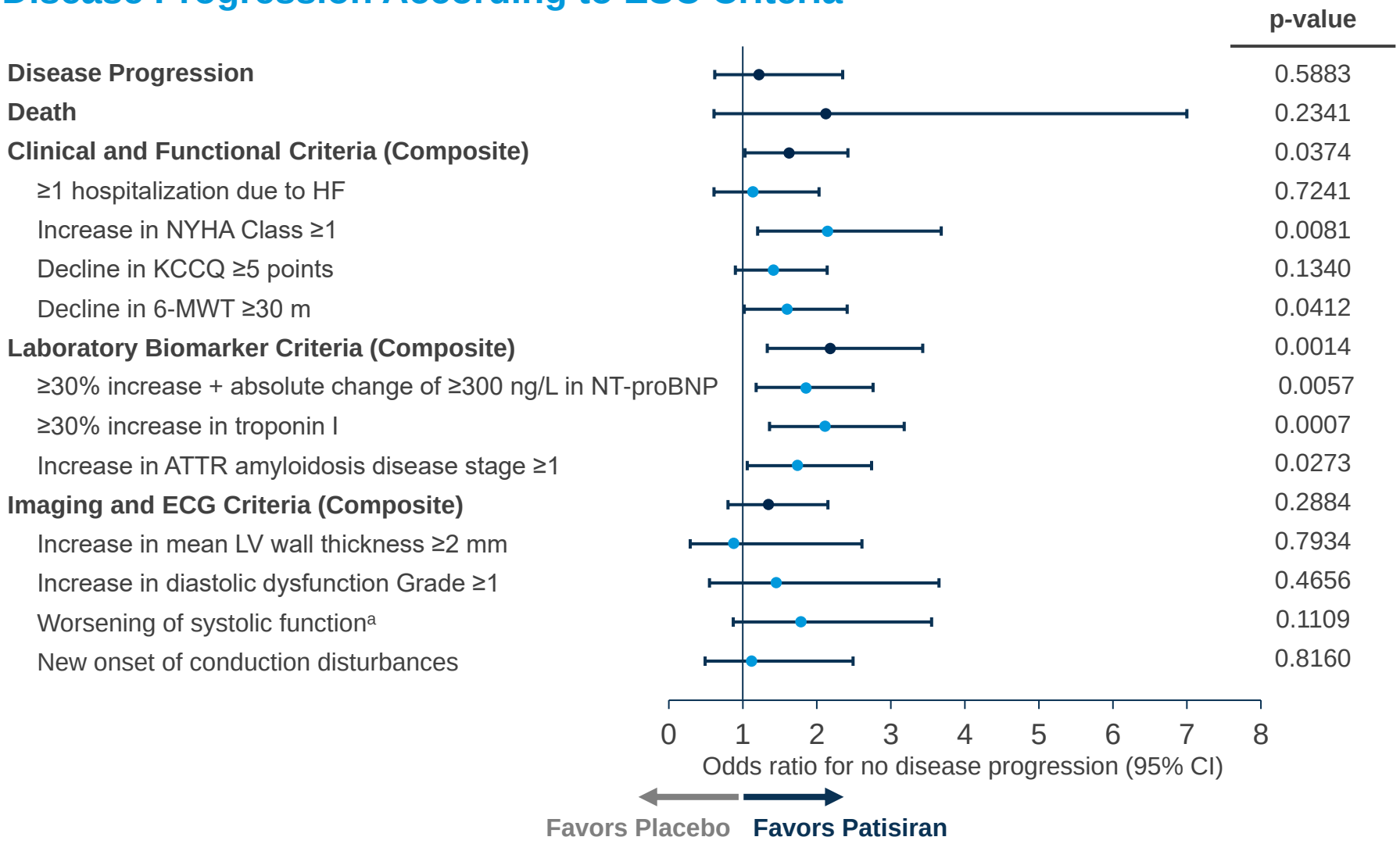
Disease Progression According to ESC Criteria

- This post hoc analysis included 180 and 178 patients in the patisiran and placebo arms, respectively
- At Month 12, treatment with patisiran improved the odds of no disease progression vs placebo (OR 1.2; 95% CI 0.62–2.35) (**Figure 3**)
- Patisiran demonstrated benefits vs placebo in the clinical and functional (odds of no disease progression vs placebo: OR 1.58; 95% CI 1.03–2.42) and laboratory biomarker (OR 2.14; 95% CI 1.33–3.43) criteria domains (**Figure 3**)
- Patisiran demonstrated a favorable trend in the imaging and ECG criteria domain (odds of no disease progression vs placebo: OR 1.31; 95% CI 0.80–2.15) (**Figure 3**)

CI, confidence interval; ECG, electrocardiography; ESC, European Society of Cardiology; OR, odds ratio.

Disease Progression According to ESC Criteria (cont'd)

Figure 3. Disease Progression According to ESC Criteria

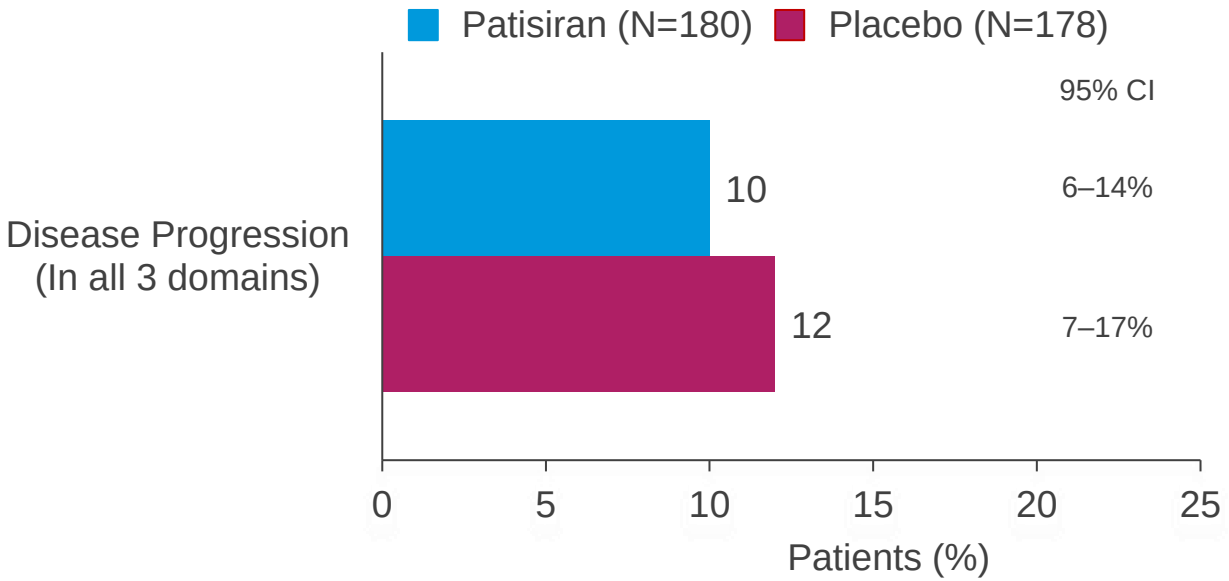


[a]Defined as decrease in LVEF ≥5%, decrease in stroke volume ≥5 mL, and ≥1% increase in average peak longitudinal strain. 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; ECG, electrocardiography; ESC, European Society of Cardiology; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association.

Disease Progression According to ESC Criteria (cont'd)

- A lower proportion of patients receiving patisiran vs placebo met the disease progression criteria across all 3 domains (**Figure 4**)
  - In the patisiran and placebo arms, respectively, 56% vs 67% of patients had disease progression according to the clinical and functional criteria, 52% vs 68% according to the laboratory biomarker criteria, and 21% vs 25% according to the imaging and ECG criteria

Figure 4. Percentage of Patients with Disease Progression in All Three Domains[a]



[a]The three ESC expert consensus domains are Clinical and Functional, Laboratory Biomarker, and Imaging and ECG. CI, confidence interval; ECG, electrocardiography; ESC, European Society of Cardiology.

Disease Progression According to ESC Criteria (cont'd)

- A numerically lower proportion of patients receiving patisiran vs placebo had disease progression according to all sub-criteria in each of the 3 domains (**Figure 5a,b,c**) apart from 2 of the imaging and ECG criteria (**Figure 5c**)
- Approximately 25% of patients who experienced disease progression after receiving placebo also reported worsening in NYHA class, compared with 13% of patients receiving patisiran (**Figure 5a**)

Figure 5a. Percentages of Patients with Disease Progression by Clinical and Functional Criteria

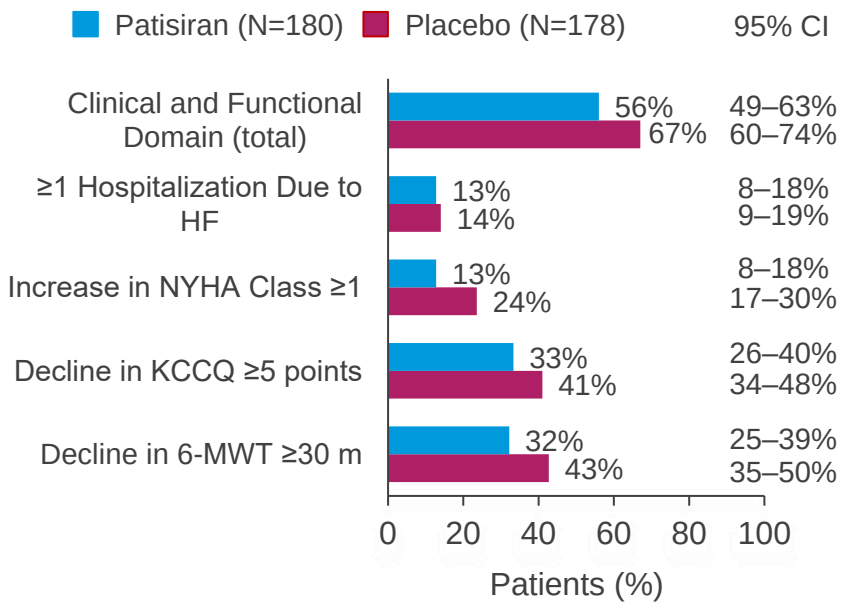


Figure 5b. Percentages of Patients with Disease Progression by Laboratory Biomarker Criteria

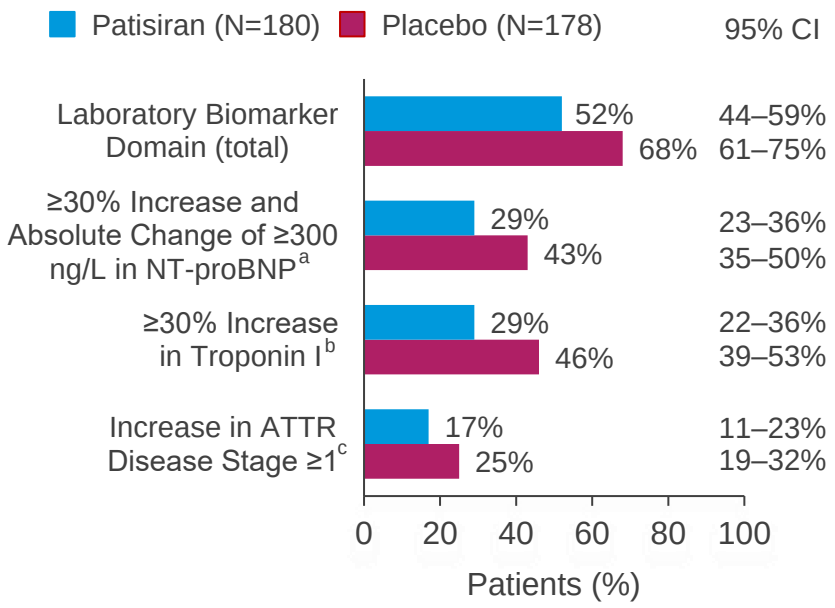
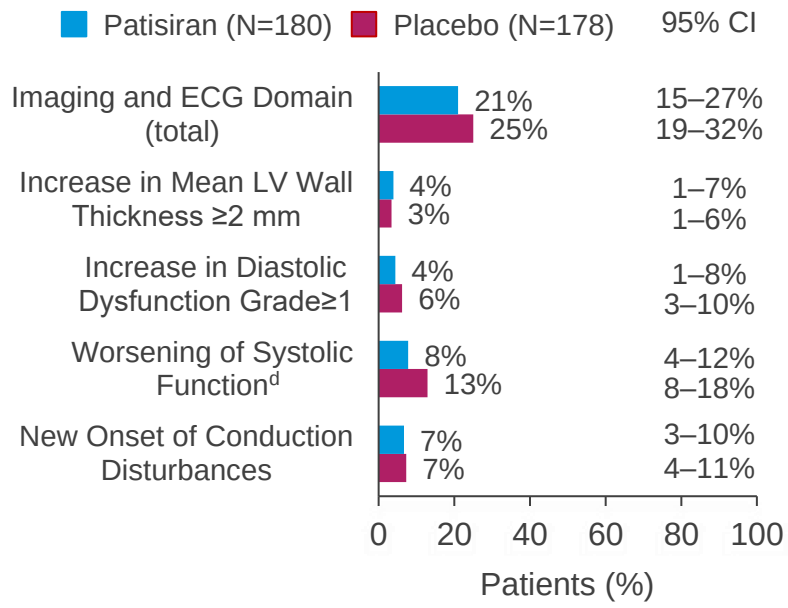


Figure 5c. Percentages of Patients with Disease Progression by Imaging and ECG Criteria



[a]Data missing for 13 and 15 patients in the patisiran and placebo arms, respectively. [b]Data missing for 22 and 23 patients in the patisiran and placebo arms, respectively. [c]Data missing for 8 and 12 patients in the patisiran and placebo arms, respectively. [a]Defined as decrease in LVEF ≥5%, decrease in stroke volume ≥5 mL, and ≥1% increase in average peak longitudinal strain. 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; ECG, electrocardiography; ESC, European Society of Cardiology; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association.

Safety

- Overall safety is shown in **Table 2**
- The majority of AEs were mild or moderate in severity
- The frequency of severe and serious adverse events was similar between groups (**Table 2**)
- AEs occurring in ≥5% of patisiran-treated patients and more frequently (≥3%) in the patisiran group included IRRs (12% vs 9%), arthralgia (8% vs 4%), and muscle spasms (7% vs 2%)
- Serious AEs reported in ≥2% of patients in the patisiran and placebo groups, respectively, were cardiac failure (8% vs 7%), atrial fibrillation (3% vs 2%), and atrioventricular block complete, amyloidosis, and syncope (each in 1% vs 2% of patients)
- None of the deaths reported were considered related to study drug

Table 2. Overall Safety Profile

≥1 Event, n (%)	Patisiran N=181	Placebo N=178
AEs	165 (91)	168 (94)
Serious AEs	61 (34)	63 (35)
Severe AEs	47 (26)	52 (29)
Cardiac AEs[a]	82 (45)	100 (56)
Cardiac serious AEs[a]	32 (18)	28 (16)
AEs leading to study drug discontinuation	5 (3)	5 (3)
Deaths[b]	5 (3)	8 (4)

[a]Cardiac AEs and serious AEs included all events selected according to the Medical Dictionary for Regulatory Activities terms for cardiac disorders System Organ Class. [b]Deaths in the patisiran group included sudden cardiac death, HF, pancreatitis, COVID-19, and undetermined death. Deaths in the placebo group included heart failure (3 patients), undetermined death (2 patients), cholangitis, infection, and pancreatic cancer. AE, adverse event; HF, heart failure; IRR, infusion-related reaction.

Conclusions

- Fewer patisiran-treated patients in APOLLO-B had evidence of disease progression vs placebo at Month 12, based on the 2021 ESC Expert Consensus on the Monitoring of Transthyretin Amyloid Cardiomyopathy
- The risk of disease progression was lower at Month 12 with patisiran vs placebo by Clinical and Functional and Laboratory Biomarker composite criteria, and trended lower by Imaging and ECG criteria from the ESC consensus
- By NYHA class and ATTR amyloidosis disease stage (Gillmore), the risk of disease progression was lower in patisiran- than placebo-treated patients
- Patisiran demonstrated an acceptable safety profile, including no cardiac safety concerns
- Long-term follow-up will further assess the impact of patisiran in patients with ATTR amyloidosis with CM

ATTR, transthyretin-mediated; CM, cardiomyopathy; ECG, electrocardiography; ESC, European Society of Cardiology; NYHA, New York Heart Association.

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