Long-term Tafamidis Efficacy in Patients With Transthyretin Amyloid Cardiomyopathy by Baseline Left Ventricular Ejection Fraction

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INTRODUCTION

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and underdiagnosed condition that leads to heart failure (HF).[1]
  - Patients with HF are categorized based on left ventricular ejection fraction (LVEF), which is used to guide treatment decisions and prognosis.
  - HF can occur with preserved LVEF (≥50%; HFpEF), mildly reduced LVEF (41–49%; HFmrEF), or reduced LVEF (≤40%; HFrEF).[2]
  - Patients with ATTR-CM present with diverse LVEF.[3,4]
- Tafamidis is approved in multiple countries worldwide for the treatment of patients with ATTR-CM.[5]
  - This approval was based on findings from the phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT; NCT01994889).[6]
  - A long-term extension (LTE) study (NCT02791230) enabled patients who completed ATTR-ACT to receive tafamidis for ≤60 months. Findings from the LTE study further support the benefit of tafamidis treatment in patients with ATTR-CM.[7]
- Current guidelines recommend tafamidis for the treatment of patients with ATTR-CM independent of their LVEF grouping. However, there remains uncertainty around the relative value of tafamidis treatment in patients with HFmrEF and HFrEF vs HFpEF.[2,8] Moreover, tafamidis is not reimbursed in some regions for patients with LVEF <50%.[9,10]
- This post hoc analysis evaluated the long-term efficacy of tafamidis by baseline LVEF (<50% or ≥50%) in patients treated with continuous tafamidis in ATTR-ACT and the LTE study vs those who received placebo in ATTR-ACT and then tafamidis in the LTE study.

METHODS

Study Design

- ATTR-ACT was a randomized, double-blind, placebo-controlled, parallel-design, international, multicenter, phase 3 trial.[6]
- Patients were stratified and randomized 2:1:2 to tafamidis meglumine 80 mg or 20 mg or placebo for 30 months alongside standard of care therapy.
- Patients 18–90 years old with biopsy confirmed ATTR-CM, end-diastolic intraventricular septal thickness >12 mm, history of HF, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥600 pg/mL, and a 6-minute walk test (6MWT) distance >100 m were eligible to enroll.
- Patients were excluded if they had New York Heart Association (NYHA) functional class IV symptoms, history of liver or heart transplantation, or an implanted cardiac device.
- After completing ATTR-ACT, patients were eligible to receive tafamidis in the LTE study.[6,7]
  - Following a protocol amendment in July 2018, all patients transitioned to tafamidis free acid 61 mg (bioequivalent to tafamidis meglumine 80 mg).

Post hoc Analysis

- This analysis included only patients who were randomized to tafamidis meglumine 80 mg (the approved dose for ATTR-CM) or placebo in ATTR-ACT.
- Time to all-cause mortality events was analyzed using a Cox proportional hazards model with treatment and transthyretin (*TTR*) genotype as covariates and visualized using Kaplan–Meier plots.
- Among patients with data at each time point, change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Symptom (KCCQ-OS) score was analyzed using a mixed model for repeated measures (MMRM) to Month 60 and 6MWT distance and NT-proBNP concentration to Month 30.
  - Treatment groups were compared using an MMRM in an unstructured covariance matrix, with treatment, visit, *TTR* genotype, and visit-by-treatment interaction as fixed effects.

RESULTS

- Of 441 patients enrolled in ATTR-ACT, 176 were randomized to tafamidis 80 mg and 177 to placebo (**Table 1**).
  - Among all patients with baseline LVEF data (n=348), 51% had an LVEF <50% and 49% had an LVEF ≥50%.

Patients With LVEF <50%

- All-cause mortality was lower with tafamidis 80/61mg vs placebo to tafamidis treatment at Months 30 and 60 and end of follow-up (**Figure 1A**, **Table 2**).
- At Month 30, change from baseline in 6MWT distance (–59.6 vs –86.5 m; P=0.071) and NT-proBNP concentration (1584.7 vs 2644.9 ng/L; P=0.188) were numerically smaller in the tafamidis 80/61 mg vs placebo group.
- Starting from Month 12 to Month 60, the change from baseline in KCCQ-OS score was significantly smaller in the tafamidis 80/61mg vs placebo to tafamidis group (**Figure 1B**).

Patients With LVEF ≥50%

- All-cause mortality was lower with tafamidis 80/61mg vs placebo to tafamidis treatment at Months 30 and 60 and end of follow-up (**Figure 2A**, **Table 2**).
- At Month 30, change from baseline in 6MWT distance (–34.6 vs –121 m; P<0.001) and NT-proBNP concentration (663.0 vs 4384.7 ng/L; P<0.0001) were statistically smaller in the tafamidis 80/61 mg group.
- Starting from Month 12 to Month 60, the change from baseline in KCCQ-OS score was significantly smaller in the tafamidis 80/61mg vs placebo to tafamidis group (**Figure 2B**).

Table 1: ATTR-ACT baseline demographics and characteristics

	LVEF <50%		LVEF ≥50%	
	Tafamidis 80/61 mg n=88	Placebo to tafamidis n=89	Tafamidis 80/61 mg n=85	Placebo to tafamidis n=86
Age, mean (SD), y	75 (7.7)	73 (6.2)	75 (6.9)	74 (7.1)
Sex, n (%)				
Male	79 (89.8)	79 (88.8)	76 (89.4)	76 (88.4)
Female	9 (10.2)	10 (11.2)	9 (10.6)	10 (11.6)
Race, n (%)				
White	64 (72.7)	71 (79.8)	69 (81.2)	73 (84.9)
Black or African American	17 (19.3)	17 (19.1)	9 (10.6)	9 (10.5)
Asian	6 (6.8)	1 (1.1)	5 (5.9)	4 (4.7)
Other[a]	1 (1.1)	0	2 (2.4)	0
mBMI, mean (SD)[b]	1054 (172.2)	1059 (191.0)	1069 (168.5)	1073 (193.4)
TTR genotype, n (%)				
Wild-type	62 (70.5)	65 (73.0)	69 (81.2)	67 (77.9)
Variant	26 (29.5)	24 (27.0)	16 (18.8)	19 (22.1)
NYHA classification, n (%)				
I	7 (8.0)	9 (10.1)	9 (10.6)	4 (4.7)
II	50 (56.8)	40 (44.9)	53 (62.4)	60 (69.8)
III	31 (35.2)	40 (44.9)	23 (27.1)	22 (25.6)
NT-proBNP concentration, mean (SD), ng/L	4644 (3537)	4298 (2868)	3222 (2351)	3396 (3047)
Troponin I concentration	n=88	n=89	n=85	n=85
Mean (SD), ng/mL	0.36 (1.32)	0.19 (0.18)	0.15 (0.10)	0.17 (0.18)
eGFR	n=72	n=73	n=76	n=75
Mean (SD), mL/min/1.73 m^2	55 (16.6)	52 (15.1)	58 (14.7)	58 (16.8)
LVEF, mean (SD), %	39.9 (7.9)	41.1 (6.3)	56.5 (4.2)	56.5 (4.7)

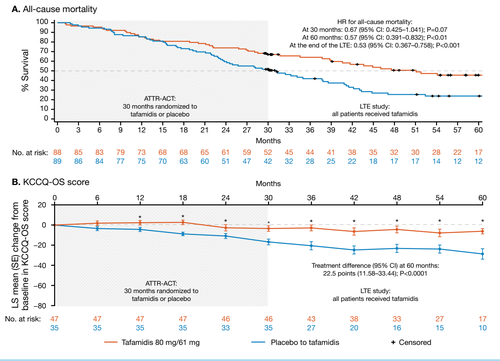
[a] Other includes American Indian or Alaskan Native.
[b] mBMI = (weight in kg / height in m^2) × serum albumin concentration in g/L.
ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; eGFR=estimated glomerular filtration rate (by Modification of Diet in Renal Disease equation); LVEF=left ventricular ejection fraction; mBMI=modified body mass index; NT-proBNP=N-terminal pro-B-type natriuretic peptide concentration; NYHA=New York Heart Association; *TTR*=transthyretin

Table 2: All-cause mortality by LVEF at ATTR-ACT baseline

	LVEF <50%		LVEF ≥50%	
	Tafamidis 80/61 mg n=88	Placebo to tafamidis n=89	Tafamidis 80/61 mg n=85	Placebo to tafamidis n=86
Follow-up duration, median (95% CI), mo	60 (55.7–74.9)	64 (54.3–NE)	63 (60.0–68.7)	61 (55.6–67.4)
All-cause mortality, n (%)	52 (59.1)	73 (82.0)	35 (41.2)	52 (60.5)
First event: n (%)				
All-cause death	45 (51.1)	69 (77.5)	33 (38.8)	50 (58.1)
Heart transplant	5 (5.7)	4 (4.5)	2 (2.4)	2 (2.3)
Implantation of a CMAD	2 (2.3)	0	0	0

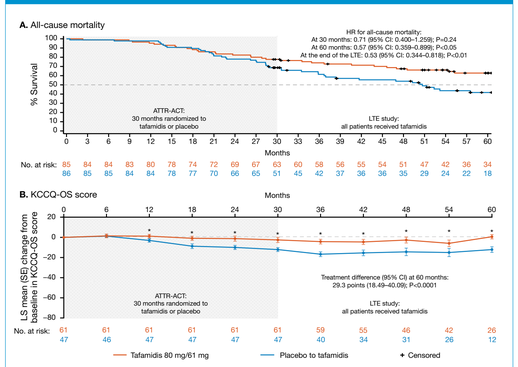
Heart transplant and implantation of a CMAD were treated as death.
ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CMAD=cardiac mechanical assist device; LVEF=left ventricular ejection fraction; NE=not estimable

Figure 1: All-cause mortality and KCCQ-OS score of patients with baseline LVEF <50%



* P<0.05
ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; HR=hazard ratio; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Symptom; LS=least squares; LTE=long-term extension; LVEF=left ventricular ejection fraction

Figure 2: All-cause mortality and KCCQ-OS score of patients with baseline LVEF ≥50%



* P<0.05
ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; HR=hazard ratio; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire-Overall Symptom; LS=least squares; LTE=long-term extension; LVEF=left ventricular ejection fraction

Limitations

- Baseline differences in disease severity make comparisons between LVEF groups challenging as patients with more advanced HF are less likely to respond to treatment.
- The treatment effect of tafamidis demonstrated in this study likely underestimated its efficacy against placebo, as patients in the comparator group (placebo to tafamidis) also received tafamidis in the LTE study.

CONCLUSIONS

- Presentation with LVEF <50% was common in patients with ATTR-CM enrolled in ATTR-ACT and its LTE study.
- Early initiation of tafamidis treatment was associated with reductions in long-term all-cause mortality and deterioration of quality of life in patients with ATTR-CM with baseline LVEF <50% or ≥50%.
  - These findings demonstrate the efficacy of tafamidis in patients with ATTR-CM, irrespective of initial LVEF.

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DISCLOSURES

BMD: Consultancy fees from Alnylam and Eidos. **TD:** Consulting fees from Alnylam, GlaxoSmithKline, Pfizer, and Prothena; honoraria from Alnylam, Pfizer, and Prothena; research grants from GlaxoSmithKline and Pfizer; and clinical trial support from Alnylam, Ionis, and Pfizer. **MH:** Honoraria for advisory board participation from Pfizer, Alnylam, Akcea, Alexion, and Eidos; and served as a speaker for a scientific meeting session funded by Alnylam. **RW** and **FSA:** Employees of Pfizer and hold stock or stock options. **PG-P:** Speaker in scientific meetings for Alnylam, BridgeBio, Ionis, Intellia, AstraZeneca, Novo Nordisk, and Pfizer; funding from Alnylam and Pfizer for scientific meeting expenses; consultancy fees from Alnylam, Attralus, BridgeBio, Neuroimmune, AstraZeneca, Novo Nordisk, Alexion, Intellia, and Pfizer; and his institution has received research grants/educational support from Alnylam, BridgeBio, AstraZeneca, Novo Nordisk, Intellia, and Pfizer.

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