Functional Stability Measured by Changes in 6-Minute Walking Distance in Patients Treated With Tafamidis vs Placebo: Post Hoc Analysis From ATTR-ACT

1154-07

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INTRODUCTION

- Tafamidis is a near-complete transthyretin (TTR) kinetic stabilizer for treating transthyretin amyloid cardiomyopathy (ATTR-CM) that is administered orally once daily and has demonstrated a statistically significant reduction in mortality at 30 months compared with placebo.[1-3]
- In the phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), tafamidis was shown to slow disease progression and prolong survival in patients with ATTR-CM.[1] Improvements in patient-reported outcomes and quality of life were also observed.[1]
- Changes in the 6-minute walking distance (6MWD) are an established indicator of functional stability or progression in ATTR-CM.[4]
  - A decline of >35 meters or >5% of 6MWD after 12 months was associated with increased mortality.[4]
  - In addition, a decline of 30–40 meters in 6MWD has been suggested as a marker of disease progression.[5-7]
- In ATTR-ACT, patients treated with tafamidis vs placebo experienced a significantly smaller decline in the 6MWD starting at Month 6 until the end of the study (P<0.001).[1]

OBJECTIVES

- Functional stability in the first year of the ATTR-ACT study, and the subsequent impact on all-cause mortality and cardiovascular (CV)-related hospitalization were analyzed from Month 12 to 30 (end of study).

METHODS

- Patients who received either tafamidis meglumine 80 mg or placebo in ATTR-ACT (NCT01994889) who were alive at Month 12 and had baseline and Month 12 6MWD data were included in this analysis.
  - Patients were categorized at Month 12 as 6MWD stable (functional stability, defined as ≤35-meter decline in 6MWD from baseline) or 6MWD progression (worsening heart failure, defined as >35-meter decline in 6MWD from baseline).
- For all-cause mortality summaries, the subsequent analysis set excluded patients who died in the first 12 months; all-cause mortality events occurring from Month 12 until Month 30 (end of the study) were analyzed.
  - All-cause mortality included heart transplants and fitting cardiac mechanical-assist devices.
- For CV-related hospitalization summaries, the subsequent analysis set excluded events that occurred during the first 12 months; CV-related hospitalization events occurring from Month 12 till Month 30 were analyzed.
- A Cox proportional hazard model with treatment as the main effect was used to evaluate time to all-cause mortality from Months 12–30 (end of study).
- A Poisson regression model with treatment as the main effect was used to evaluate CV-related hospitalization rates (as adjudicated by the endpoint adjudication committee) from Months 12–30.
- Both models were adjusted for *TTR* genotype (variant or wild-type) and New York Heart Association (NYHA) functional class at baseline, including missing NYHA classifications.

RESULTS

Patient Characteristics

- Baseline characteristics were generally balanced and are summarized in **Table 1**.

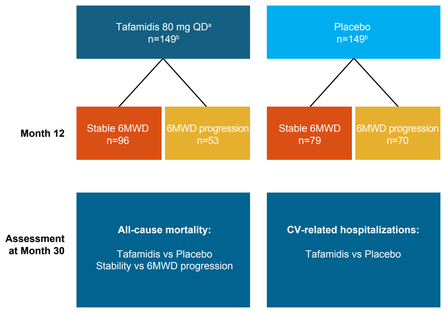
Table 1: Baseline characteristics by 6MWD status at Month 12

	Tafamidis 80 mg (n=149)		Placebo (n=149)	
6MWD status at Month 12	6MWD stable n=96 (64.4%)	6MWD progression n=53 (35.6%)	6MWD stable n=79 (53.0%)	6MWD progression n=70 (47.0%)
Age, mean (SD), y	74.6 (6.9)	74.9 (7.6)	73.5 (7.4)	74.3 (6.0)
Male, n (%)	84 (87.5)	50 (94.3)	70 (88.6)	66 (94.3)
Genotype, n (%)				
Wild-type	76 (79.2)	42 (79.2)	65 (82.3)	55 (78.6)
Variant	20 (20.8)	11 (20.8)	14 (17.7)	15 (21.4)
Medical history, n (%)				
AF/AFL	56 (58.3)	38 (71.7)	52 (65.8)	45 (64.3)
IHD	7 (7.3)	2 (3.8)	2 (2.5)	3 (4.3)
Stroke	0	0	0	2 (2.9)
COPD	4 (4.2)	2 (3.8)	4 (5.1)	7 (10.0)
Diabetes mellitus	14 (14.6)*	2 (3.8)*	14 (17.7)	14 (20.0)
NYHA class, n (%)				
I	10 (10.4)	5 (9.4)	5 (6.3)	8 (11.4)
II	60 (62.5)	33 (62.3)	51 (64.6)	40 (57.1)
III	26 (27.1)	15 (28.3)	23 (29.1)	22 (31.4)
ODI, n (%)	38 (39.6)†	31 (58.5)†	40 (50.6)	43 (61.4)
NT-proBNP, median (range), pg/mL	2688.0 (392.0–12009.9)	2995.7 (857.0–12379.9)	2897.4 (543.9–16599.9)	2828.0 (298.0–16786.8)
KCCQ-OSS, median (range)	72.4 (21.4–100.0)	71.6 (7.6–100.0)	75.1 (16.7–97.9)	68.2 (19.8–100.0)
6MWD, median (range), m	376.5 (118.0–665.0)	360.0 (110.0–685.0)	360.0 (80.0–680.0)	394.0 (200.0–822.0)
BMI, mean (SD), kg/m^2	26.0 (3.3)	26.0 (3.3)	26.5 (4.3)	26.1 (4.2)
Median follow-up (Q1, Q3), months	17.9 (17.7, 18.1)	17.8 (14.8, 18.1)	17.8 (16.8, 18.1)	17.6 (10.1, 18.0)

* P=0.0413; P value obtained from t-test to compare the means.
† P=0.0267; P value obtained from chi-square for binary or categorical variables.
6MWD stable: ≤35 meters decline from baseline at Month 12 after receiving tafamidis or placebo.
6MWD progression: >35 meters decline from baseline at Month 12 after receiving tafamidis or placebo.
6MWD=6-minute walking distance; AF/AFL=atrial fibrillation/flutter; BMI=body mass index; COPD=chronic obstructive pulmonary disease; IHD=ischemic heart disease; KCCQ-OSS=Kansas City Cardiomyopathy Questionnaire Overall Summary Score; NYHA=New York Heart Association; NT-proBNP=N-terminal pro–B-type natriuretic peptide; ODI=outpatient diuretic intensification; Q=quartile

- In the tafamidis 80 mg and placebo groups, 64% (n=96/149) and 53% (n=79/149) of patients, respectively, had stable 6MWD after 12 months (**Figure 1**).

Figure 1: Design of this 6MWD post hoc analysis



[a] Approved dose for the treatment of ATTR-CM.
[b] Number of patients included in this analysis.
Stable 6MWD: ≤35-meter decline from baseline at Month 12 after receiving tafamidis or placebo.
6MWD progression: >35-meter decrease from baseline at Month 12 after receiving tafamidis or placebo.
6MWD=6-minute walking distance; ATTR-CM=transthyretin amyloid cardiomyopathy; CV=cardiovascular; QD=once daily

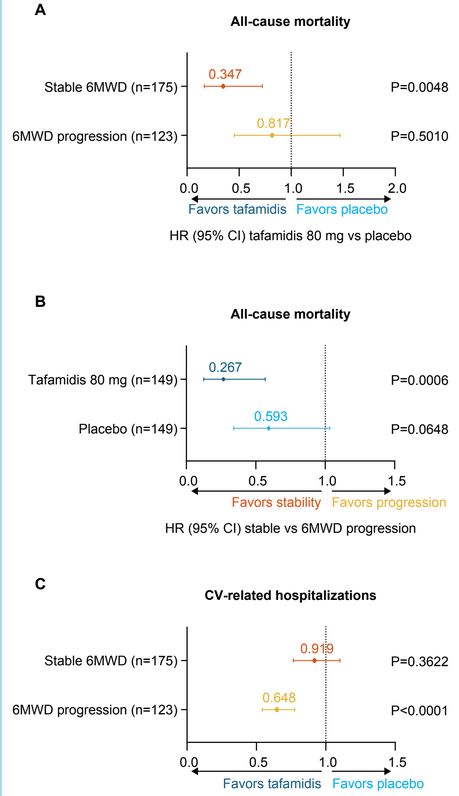
All-Cause Mortality

- At Month 30, incidence of all-cause mortality was lower in patients with 12-month stable 6MWD vs 6MWD progression in both treatment arms: 11% vs 34% in the tafamidis and 28% vs 43% in the placebo groups.
  - Incidence of all-cause mortality was numerically higher in the placebo 6MWD subgroups vs the corresponding tafamidis subgroups (28% vs 11% in the stable 6MWD and 43% vs 34% in the 6MWD progression subgroups).
- Among all patients with stable 6MWD, a 65% reduction in the risk of all-cause mortality was observed for patients receiving tafamidis 80 mg compared with placebo (hazard ratio [HR] tafamidis vs placebo 0.347 [95% CI: 0.166, 0.724]; P=0.0048); a non-significant reduction was seen in patients with 6MWD progression (**Figure 2A**).
- The impact of 12-month 6MWD status on all-cause mortality was analyzed for each treatment arm.
  - In patients receiving tafamidis 80 mg, a 73% hazard reduction was observed for stable 6MWD (HR vs progression: 0.267 [95% CI: 0.125, 0.568]; P=0.0006). A non-significant hazard reduction with stable 6MWD was observed in patients receiving placebo (**Figure 2B**).

CV-Related Hospitalizations

- Incidence and yearly rates of CV-related hospitalizations were lower in patients with stable 6MWD than those with progression in both treatment arms:
  - With tafamidis 80 mg, incidence of CV-related hospitalizations in the stable 6MWD and progression groups, respectively, was 41% and 68% and yearly model adjusted rates were 0.74 and 0.87.
  - With placebo, incidence of CV-related hospitalizations was 57% and 67% in the stable 6MWD and progression groups, respectively. Respective annual model adjusted rates of 0.79 and 1.29 were numerically higher with placebo compared with the corresponding tafamidis 80 mg subgroups.
- Among patients with 6MWD progression, a 35% reduction in risk of CV-related hospitalizations was observed in patients who received tafamidis 80 mg (risk ratio vs placebo 0.648 [95% CI: 0.542, 0.776]; P<0.0001); this treatment benefit was not observed in patients with stable 6MWD (**Figure 2C**).

Figure 2: (A) Time to all-cause mortality: tafamidis vs placebo, (B) time to all-cause mortality: stable 6MWD vs 6MWD progression, and (C) time to CV-related hospitalizations: tafamidis vs placebo



Stable 6MWD: ≤35-meter decline from baseline at Month 12 after receiving tafamidis 80 mg or placebo. 6MWD progression: >35-meter decrease from baseline at Month 12 after receiving tafamidis or placebo.
6MWD=6-minute walking distance; CV=cardiovascular; HR=hazard ratio; RR=risk ratio

CONCLUSIONS

- The proportion of patients with stable 6MWD after 1 year was greater in the tafamidis meglumine 80 mg group compared with placebo.
- During the subsequent 18 months of follow-up, the risk of all-cause mortality was significantly lower in patients receiving tafamidis meglumine 80 mg with stable 6MWD compared with placebo.
- The risk of CV-related hospitalization was significantly reduced in patients with 6MWD progression receiving tafamidis meglumine 80 mg compared with placebo.
- Limitations include the post hoc nature of this analysis, the small sample size, and potential survivorship bias by including only patients who survive the first 12 months of the study.
- These findings support the hypothesis that treatment plays an important role in maintaining functional stability and improving outcomes for patients with ATTR-CM.

REFERENCES

1. Maurer MS, et al. N Engl J Med 2018;379:1007-16. **2**. Nelson LT, et al. Amyloid 2021;28:24-9. **3**. Tess DA, et al. Amyloid 2023;30:208-19. **4**. Ioannou A, et al. J Am Coll Cardiol 2024;84:43-58. **5**. Ioannou A. Heart Int 2025;19:20-5. **6**. Garcia-Pavia P, et al. JACC Heart Fail 2026;14:102766. **7**. Garcia-Pavia P, et al. Eur J Heart Fail 2021;23:895-905.

DISCLOSURES

RW: Adviser: Alexion, Alnylam, AstraZeneca, BridgeBio, Novo Nordisk, Pfizer. **MAH:** Advisory board: Akcea, Alexion Pharmaceuticals, Alnylam, BridgeBio, Pfizer, one-time speaker for Alnylam. **MG:** Institutional research funding: Alnylam Pharmaceuticals, AstraZeneca, Eidos Therapeutics, Janssen Pharmaceuticals, Novo Nordisk, Pfizer; institutional advisory board or consultation fees: AstraZeneca, Eidos Therapeutics, Janssen Pharmaceuticals, Pfizer. **PGP:** Speaker fees: Alnylam, AstraZeneca, Bayer, BridgeBio, Intellia, Ionis, Novo Nordisk, Pfizer; scientific meeting expenses: Alnylam, Bayer, Pfizer; consultancy fees: Alexion, Alnylam, AstraZeneca, Attralus, Bayer, BridgeBio, Intellia, Ionis, Neuroimmune, Novo Nordisk, Pfizer; institution received research grants/educational support: Alnylam, AstraZeneca, Bayer, BridgeBio, Intellia, Novo Nordisk, Pfizer. **VM, RW:** Employees of and hold stock/options in Pfizer.

ACKNOWLEDGMENTS

This study was sponsored by Pfizer. Medical writing support was provided by Andrea Schauenburg of Engage Scientific Solutions and was sponsored by Pfizer. The authors would like to thank the participants of the ATTR-ACT and the long-term extension.

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Presented at the American College of Cardiology (ACC) 75th Annual Scientific Session & Expo, March 28–30, 2026, New Orleans, LA, USA