Tafamidis Efficacy Among Octogenarian Patients in the Phase 3 ATTR-ACT and Ongoing Long-Term Extension Study

Pablo Garcia-Pavia[1-3], Marla B Sultan[4], Balarama Gundapaneni[5], Yoshiki Sekijima[6], Federico Perfetto[7], Mazen Hanna[8], Ronald Witteles[9]

[1]Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, CIBERCV, Madrid, Spain; [2]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; [3]Universidad Francisco de Vitoria (UFV), Pozuelo de Alarcón, Madrid, Spain; [4]Pfizer Inc, New York, NY, USA; [5]Pfizer Inc, Groton, CT, USA; [6]Shinshu University School of Medicine, Matsumoto, Japan; [7]Tuscan Regional Amyloid Referral Centre, Careggi University Hospital, Florence, Italy; [8]Cleveland Clinic, Cleveland, OH, USA; [9]Stanford University School of Medicine, Stanford, CA, USA

INTRODUCTION

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive condition that leads to heart failure.[1]
  - ATTR-CM is commonly diagnosed in older patients; particularly wild-type ATTR-CM, which is associated with aging and has a median age at onset of ~75 years.[2,3]
- Tafamidis was approved to treat patients with ATTR-CM based on findings from the phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT; NCT01994889).[4]
  - Patients who completed ATTR-ACT could receive tafamidis in an open-label, long-term extension (LTE) study (NCT02791230) for an additional ≤60 months.
  - Findings from the LTE study further supported the benefit of tafamidis treatment in patients with ATTR-CM.[5]
- Despite approval without age restrictions by the US Food and Drug Administration and the European Medicines Agency, characteristics such as a limited remaining lifespan, comorbidities, frailty, and polypharmacy are common in elderly patients with ATTR-CM and influence decisions around the initiation of tafamidis.[6-8]
- This post hoc analysis examined the long-term benefit of tafamidis in patients with ATTR-CM aged <80 and ≥80 years using data from ATTR-ACT and interim data from the LTE study.[9]

METHODS

Study Design

- ATTR-ACT was a multicenter, international, randomized, double-blind, placebo-controlled, parallel-design, phase 3 trial in patients with ATTR-CM.[4]
- Patients were randomized to tafamidis meglumine 80 mg or 20 mg or placebo (2:1:2) for 30 months, stratified by transthyretin (*TTR*) genotype (wild-type or variant) and New York Heart Association (NYHA) class I or II/III.
- To enroll, patients (aged 18–90 years) were required to have biopsy confirmed ATTR-CM, end-diastolic intraventricular septal thickness >12 mm, history of heart failure, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥600 pg/mL, and a 6-minute walk test (6MWT) distance >100 m.
- Patients were excluded if they had NYHA class IV symptoms, a history of liver or heart transplantation, an implanted cardiac device, an estimated glomerular filtration rate <25 mL/min/1.73 m^2 or a modified body mass index (mBMI) <600.
- After completing ATTR-ACT, patients were eligible to receive tafamidis for up to 60 months in the LTE study.[4,5]
  - Following a protocol amendment in July 2018, all patients transitioned to tafamidis free acid 61 mg, which is bioequivalent to tafamidis meglumine 80 mg.

Post hoc Analysis

- This analysis included only patients randomized to tafamidis meglumine 80 mg (the approved dose for ATTR-CM) or placebo in ATTR-ACT.[9]
- Efficacy measures summarized in patients aged <80 or ≥80 years at the ATTR-ACT baseline included:
  - Change from baseline in 6MWT distance and NT-proBNP concentration to the end of ATTR-ACT.
  - Change from baseline in Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score to the interim analysis of the LTE study (August 1, 2021).
  - Cardiovascular (CV)-related hospitalizations to the end of ATTR-ACT.
  - All-cause mortality to the interim analysis of the LTE study.

RESULTS

- In ATTR-ACT, 353 patients were randomized to receive tafamidis meglumine 80 mg (n=176) or placebo (n=177), of which 25% were aged ≥80 years (**Table 1**).
  - A higher proportion of patients aged ≥80 vs <80 years had wild-type ATTR-CM (83% vs 74%) and NYHA class III symptoms (42% vs 31%) (**Table 1**).

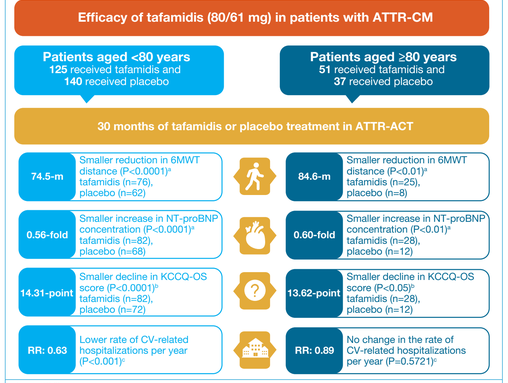
Table 1: Baseline demographics and clinical characteristics by patient age

	Aged <80 years		Aged ≥80 years	
n (%)[a]	Tafamidis 80 mg n=125	Placebo n=140	Tafamidis 80 mg n=51	Placebo n=37
Age, y				
Mean (SD)	72.0 (6.0)	71.8 (5.6)	83.0 (2.2)	82.4 (2.5)
Sex				
Male	111 (88.8)	126 (90.0)	47 (92.2)	31 (83.8)
Female	14 (11.2)	14 (10.0)	4 (7.8)	6 (16.2)
Race				
White	96 (76.8)	116 (82.9)	40 (78.4)	30 (81.1)
Black	21 (16.8)	20 (14.3)	5 (9.8)	6 (16.2)
Asian	7 (5.6)	4 (2.9)	4 (7.8)	1 (2.7)
Other	1 (0.8)	0	2 (3.9)	0
mBMI[b], mean (SD)	1098.2 (167.0)	1079.6 (196.1)	981.7 (158.7)	1016.5 (181.9)
TTR genotype				
Wild-type	90 (72.0)	105 (75.0)	44 (86.3)	29 (78.4)
Variant	35 (28.0)	35 (25.0)	7 (13.7)	8 (21.6)
NYHA class				
I/II	87 (69.6)	97 (69.3)	34 (66.7)	17 (45.9)
III	38 (30.4)	43 (30.7)	17 (33.3)	20 (54.1)
NT-proBNP, median (LQ, UQ), pg/mL	2680.5 (1746.6, 4494.0)	3015.0 (1848.0, 4575.2)	4006.8 (2625.0, 6180.5)	3828.0 (2329.0, 5305.1)
Troponin I, median (LQ, UQ), ng/mL	0.14 (0.09, 0.18)	0.14 (0.08, 0.19)	0.16 (0.09, 0.26)	0.14 (0.07, 0.19)
6MWT distance, mean (SD), m	366.5 (118.0)	369.8 (129.8)	291.7 (109.9)	290.5 (86.4)
KCCQ-OS score, mean (SD)	68.5 (21.3)	66.3 (22.2)	63.9 (21.0)	64.4 (20.2)

[a] Unless otherwise indicated.
[b] mBMI = (weight in kg/height in m^2) × serum albumin concentration in g/L.
6MWT=6-minute walk test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LQ=lower quartile; mBMI=modified body mass index; NT-proBNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; *TTR*=transthyretin; UQ=upper quartile
The results of this analysis have been published.[9]

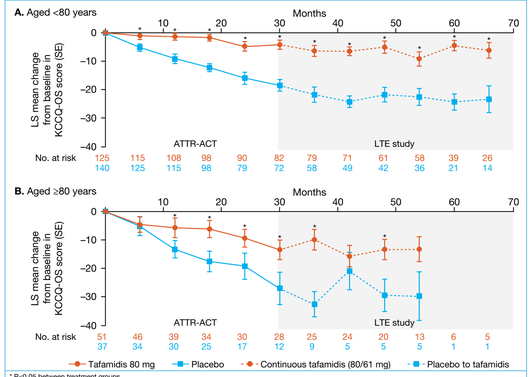
- After 30 months in ATTR-ACT, patients aged <80 and ≥80 years showed signs of disease progression that was attenuated with tafamidis treatment.
  - Reductions in 6MWT distance (least squares [LS] mean change from baseline: −50 and −71 m vs −125 and −156 m) and increases in NT-proBNP concentration (1.3 and 1.2 pg/mL vs 2.2 and 2.0 pg/mL) were significantly smaller in patients treated with tafamidis vs placebo in both age groups (**Figure 1**).
  - Across age groups, tafamidis vs placebo was associated with statistically smaller decline in KCCQ-OS score (LS mean change from baseline: −4.2 and −13.2 vs −18.5 and −26.8) (**Figure 1** and **2**).
  - In patients aged <80 years, tafamidis vs placebo was associated with a lower rate of CV-related hospitalizations per year (mean: 0.44 vs 0.70, rate ratio [95% CI]: 0.63 [0.50-0.80]; **Figure 1**).
- At the LTE study interim analysis, median follow-up duration was 60 months in patients aged ≥80 years treated with continuous tafamidis and 56 months in those initially treated with placebo in ATTR-ACT. Median follow-up times in patients aged <80 years were 61 and 60 months, respectively.
  - Patients aged <80 years treated continuously with tafamidis had a significantly smaller decline in KCCQ-OS score (**Figure 2A**) and longer median survival (**Figure 3A**) vs those initially receiving placebo in ATTR-ACT.
  - Patients aged ≥80 years treated continuously with tafamidis had a smaller decline in KCCQ-OS score (**Figure 2B**) and trended towards longer median survival (**Figure 3B**) vs those initially treated with placebo in ATTR-ACT.

Figure 1: Tafamidis efficacy in patients aged <80 and ≥80 years in ATTR-ACT



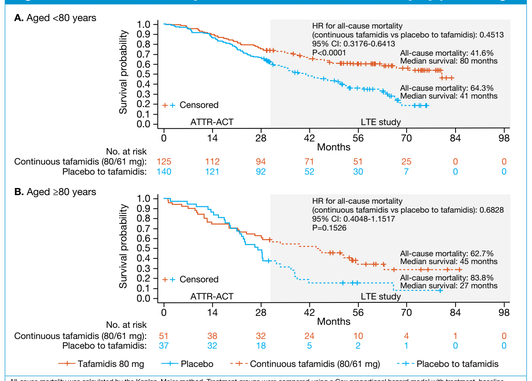
Tafamidis (80/61 mg) and placebo groups were compared using:
[a] An MMRM with an unstructured covariance matrix with center and patient within center as random effects, and treatment, visit, *TTR* genotype, and visit-by-treatment interaction as fixed effects, and baseline score as covariate.
[b] An MMRM with an unstructured covariance matrix, with treatment, visit, *TTR* genotype, and visit-by-treatment interaction as fixed effects.
[c] A Poisson regression analysis with treatment, *TTR* genotype, baseline NYHA functional class (I/II combined or III), treatment by *TTR* interaction, and treatment by NYHA functional class interaction as factors adjusted for treatment duration.
6MWT=6-minute walk test; ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; ATTR-CM=transthyretin amyloid cardiomyopathy; CV=cardiovascular; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; MMRM=mixed model for repeated measures; NTpro-BNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; RR=rate ratio; *TTR*=transthyretin
The results of this analysis have been published.[9]

Figure 2: KCCQ-OS score in ATTR-ACT and the LTE study by patient age



* P<0.05 between treatment groups.
KCCQ-OS scores were collected up to the interim analysis of the LTE study (August 1, 2021), but analysis of LS mean change stopped at Month 66 because of low numbers.
Patients in the continuous tafamidis group took 80 mg tafamidis in ATTR-ACT and tafamidis in the LTE study. Patients in the placebo to tafamidis group took placebo in ATTR-ACT and tafamidis in the LTE study.
ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; LS=least squares; LTE=long-term extension
The results of this analysis have been published.[9]

Figure 3: All-cause mortality in ATTR-ACT and the LTE study by patient age



All-cause mortality was calculated by the Kaplan-Meier method. Treatment groups were compared using a Cox proportional hazard model with treatment, baseline NYHA class (I/II combined and III), and *TTR* genotype as covariates. Heart transplantation or implantation of a CMAD were treated as death. There were 52 events in the continuous tafamidis group in patients aged <80 years (comprising 43 deaths, 7 heart transplantations, 2 CMAD implantations). Respective values in the placebo to tafamidis group in patients aged <80 years, the continuous tafamidis group in patients aged ≥80 years, and the placebo to tafamidis group in patients aged ≥80 years are 90, 84, 6, 0; 32, 32, 0, 0; and 31, 31, 0, 0.
ATTR-ACT=Tafamidis in Transthyretin Cardiomyopathy Clinical Trial; CMAD=cardiac mechanical assist device; HR=hazard ratio; NYHA=New York Heart Association; LTE=long-term extension; *TTR*=transthyretin
The results of this analysis have been published.[9]

Limitations

- There were low patient numbers towards the interim analysis of the LTE study, especially in patients aged ≥80 years.
- The ability to demonstrate the full value of long-term tafamidis treatment is limited in this study, as all patients in the LTE study received tafamidis.

CONCLUSIONS

- In ATTR-ACT, patients with ATTR-CM aged <80 and ≥80 years who received tafamidis generally had better outcomes vs those who received placebo, across several efficacy measures.
- In the LTE study, patients continuously treated with tafamidis maintained a smaller decline in KCCQ-OS score and overall had longer survival than those treated with placebo in ATTR-ACT across age groups.
- These findings demonstrated the efficacy of tafamidis across age groups of patients with ATTR-CM, including those aged ≥80 years.

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DISCLOSURES

P-GP: Speaker in scientific meetings for Alexion, Alnylam, BridgeBio, Ionis, AstraZeneca, Novo Nordisk, and Pfizer; funding for scientific meeting expenses from Alnylam and Pfizer; 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, AstraZeneca, BridgeBio, Intellia, and Pfizer. **MS and BG:** Full-time employees of Pfizer and hold stock/stock options. **YS:** Holds a patent concerning tafamidis; honoraria for lectures and advisory board participation from Pfizer and Alnylam; and his institution has received research grants from Pfizer and Alnylam. **FP:** Honoraria for advisory board participation from Pfizer, Alnylam, and Akcea. **MH:** Honoraria for advisory board participation from Pfizer, Alnylam, Akcea, Alexion, and Eidos; and speaker for a scientific meeting session funded by Alnylam. **RW:** Honoraria for advisory board participation from Pfizer, Alnylam, Ionis, AstraZeneca, Janssen, Intellia, BridgeBio, Novo Nordisk, and Alexion.

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