Tafamidis 80 mg Is More Likely to Improve Disease Measures Than Placebo in Patients With Transthyretin Amyloid Cardiomyopathy

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INTRODUCTION

- Tafamidis meglumine 80 mg and bioequivalent tafamidis free acid 61 mg are approved treatment for patients with transthyretin amyloid cardiomyopathy (ATTR-CM) in many regions worldwide.[1]
- This approval is largely based on findings from the phase 3 Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT; NCT01994889).[2]
- In a post hoc analysis of ATTR-ACT data, patients who took tafamidis meglumine 80 mg or 20 mg (pooled) vs placebo for 30 months had a significantly higher odds of improvement in a range of disease measures[3]:
  - 6-minute walk test (6MWT) distance,
  - Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score,
  - N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, and
  - Patient Global Assessment (PGA) of overall health.
- This analysis evaluated improvement in disease measures among patients who took the approved dose of tafamidis meglumine (80 mg) or placebo in ATTR-ACT.

METHODS

Studies

- ATTR-ACT (NCT01994889) was an international, randomized, placebo-controlled, parallel-design phase 3 study of tafamidis meglumine (20 mg and 80 mg) in patients with ATTR-CM.[2]
  - To enroll, patients must have been aged 18–90 years with:
    - biopsy-confirmed ATTR-CM,
    - history of heart failure,
    - NT-proBNP concentration ≥600 pg/mL, and
    - 6MWT distance >100 m at baseline.
  - Patients were excluded if they had New York Heart Association (NYHA) class IV symptoms, a history of liver or heart transplantation, or an implanted cardiac device.
  - Randomization (2:1:2) to daily oral tafamidis meglumine 80 mg, 20 mg, or placebo was stratified by transthyretin (*TTR*) genotype and NYHA functional class (I or II/III).
  - Treatment continued for 30 months.
- Patients discontinued ATTR-ACT for a number of reasons, including death, unwillingness to continue in the trial, poor tolerability/adverse events, organ transplantation or implantation of a cardiac mechanical assist device, and protocol violations.[2]

Analysis

- This analysis calculated the proportion of patients who received tafamidis meglumine 80 mg or placebo treatment and showed improvement from baseline in each of 4 disease measures at timepoints throughout ATTR-ACT (**Table 1**).
- The odds ratio (OR) for improvement was calculated at each timepoint with 95% CI and associated P value.
- Additional analyses included patients with missing data imputed as not improved.
- Patients who were randomized to tafamidis meglumine 20 mg in ATTR-ACT are not included in this analysis.[1]

Table 1: Definitions of improvement

Disease measure	Range	Definition of improvement
6MWT distance	Continuous, with longer distances indicating better functional health	Change >0
KCCQ-OS score	0 to 100; higher score indicates better HRQoL	Change >0
NT-proBNP concentration	Continuous; higher concentrations indicate worse heart failure	Change <0
PGA of overall health	7 categorical responses describing how the patient feels about their health status vs baseline	Responses of "minimally improved", "much improved", or "very much improved"

6MWT=6-minute walk test; HRQoL=health-related quality of life; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PGA=Patient Global Assessment

RESULTS

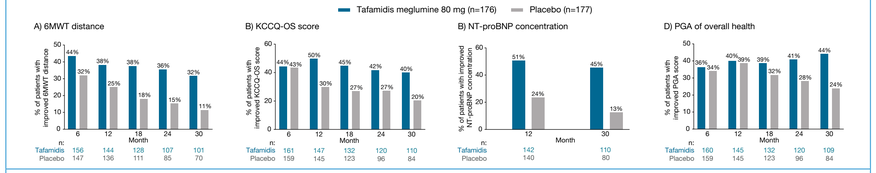
- Baseline demographics and clinical characteristics were balanced between the randomized treatment groups (**Table 2**).[2,4]
- Higher proportions of patients receiving tafamidis meglumine 80 mg (n=176 at baseline) than placebo (n=177) showed improvement in 6MWT distance, KCCQ-OS score, NT-proBNP concentration, and PGA of overall health at all timepoints (**Figure 1**).
- The OR for improvement was significantly in favor of tafamidis meglumine 80 mg treatment at all timepoints for 6MWT distance and NT-proBNP concentration, and all but Month 6 for KCCQ-OS score (**Figure 2**).
- At Month 30, the odds of improvement were statistically higher among patients taking tafamidis meglumine 80 mg vs placebo for all disease measures (**Figure 2**).
- These findings were similar when patients with missing data were imputed as not improved (**Figures 3** and **4**).

Table 2: Baseline demographics and clinical characteristics

	Tafamidis 80 mg n=176	Placebo n=177
Age, mean (SD), years	75 (7.2)	74 (6.7)
Male sex, n (%)	158 (89.8)	157 (88.7)
Race, n (%)		
White	136 (77.3)	146 (82.5)
Black	26 (14.8)	26 (14.7)
Asian	11 (6.3)	5 (2.8)
Other	3 (1.7)	0
TTR genotype, n (%)		
Wild-type	134 (76.1)	134 (75.7)
Variant	42 (23.9)	43 (24.3)
NYHA class, n (%)		
I/II	121 (68.7)	114 (64.4)
III	55 (31.3)	63 (35.6)
6MWT distance, median (min, max), m	342.5 (61.0, 685.0)	346.0 (80.0, 822.0)
KCCQ-OS score, median (min, max)	71.0 (7.6, 100.0)	68.0 (13.8, 100.0)
NT-proBNP, median (min, max), pg/mL	3122.0 (392.0, 22,020.1)	3161.0 (298.0, 16,787.1)

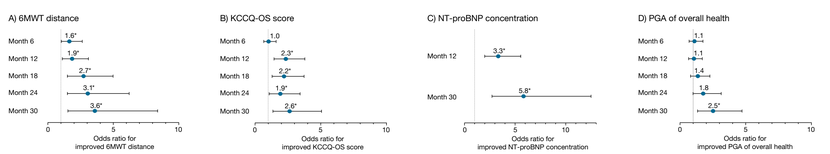
Most values have been previously published.[4]
6MWT=6-minute walk test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; max=maximum; min=minimum; NTpro-BNP=N-terminal pro-B-type natriuretic peptide; NYHA=New York Heart Association; *TTR*=transthyretin

Figure 1: Proportion of patients showing improvement



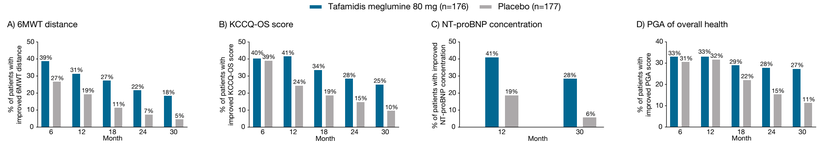
6MWT=6-minute walk test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PGA=Patient Global Assessment

Figure 2: Odds ratio for improvement with tafamidis meglumine 80 mg vs placebo treatment



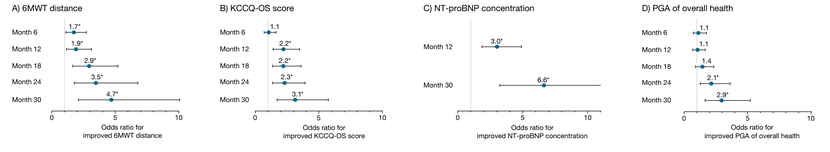
* P<0.05
6MWT=6-minute walk test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PGA=Patient Global Assessment

Figure 3: Proportion of patients showing improvement when missing data are imputed as not improved



6MWT=6-minute walk test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PGA=Patient Global Assessment

Figure 4: Odds ratio for improvement with tafamidis meglumine 80 mg vs placebo treatment when missing data are imputed as not improved



* P<0.05
6MWT=6-minute walk test; KCCQ-OS=Kansas City Cardiomyopathy Questionnaire Overall Summary; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PGA=Patient Global Assessment

CONCLUSIONS

- Patients who received tafamidis meglumine 80 mg vs placebo had a higher likelihood of improvement in a range of disease measures after 30 months of treatment in ATTR-ACT.
- These findings provide further evidence to support the efficacy of the approved tafamidis dose in patients with ATTR-CM.

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DISCLOSURES

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