Primary Endpoint Efficacy Results in the ATTRibute-CM Study: Prespecified Sensitivity Analyses Addressed Tafamidis Use

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OBJECTIVE

- **To evaluate the potential effect of concomitant tafamidis on the efficacy of acoramidis as assessed by the four-step hierarchical primary efficacy endpoint in the phase 3 ATTRibute-CM study (NCT03860935), which enrolled participants with transthyretin amyloid cardiomyopathy (ATTR-CM)**

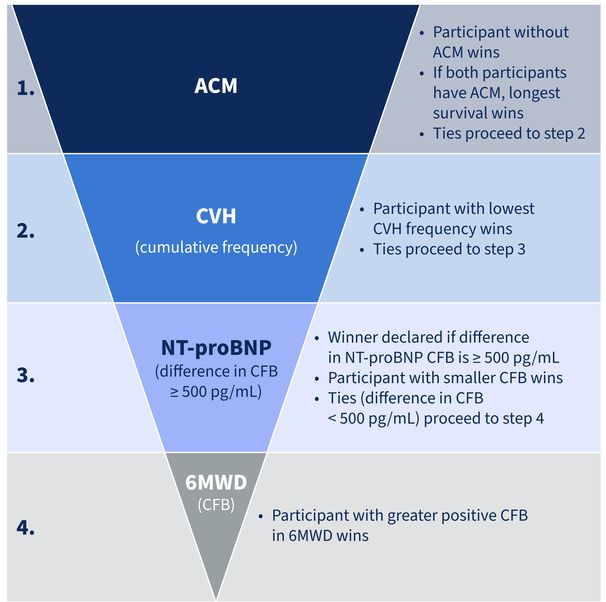
BACKGROUND

- ATTR-CM is a progressive disease characterized by the destabilization of transthyretin (TTR) and aggregation of amyloid fibrils in the heart, leading to progressive heart failure, significantly impaired quality of life, hospitalization, and death[1–3]
- Acoramidis, a highly selective, oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved by the FDA for the treatment of the cardiomyopathy of wild-type or variant ATTR-CM in adults to reduce cardiovascular death and cardiovascular-related hospitalization (CVH). Acoramidis is also approved in Europe for the treatment of wild-type or variant ATTR-CM in adults[4–6]
- In the pivotal phase 3 ATTRibute-CM study in ATTR-CM, acoramidis met its four-step primary efficacy endpoint of all-cause mortality (ACM), frequency of CVH, the difference between participants in change from baseline (CFB) in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and CFB in 6-minute walk distance (6MWD), compared with placebo ($p < 0.0001$)[7]
- The study design of ATTRibute-CM has been described previously[7]
  - Briefly, participants with ATTR-CM aged 18–90 years were randomized 2:1 to receive acoramidis HCl (800 mg) or matching placebo twice daily for 30 months[7]
  - Efficacy analyses were conducted in the modified intention-to-treat (mITT) population, which consisted of all randomized participants who had received at least one dose of acoramidis or placebo, had at least one efficacy evaluation after baseline, and had a baseline estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2
  - Once participants had completed at least 12 months of blinded study treatment, they were permitted to initiate concomitant treatment with open-label tafamidis
  - Overall, 17.5% of participants in the mITT population received tafamidis (acoramidis, 14.9%; placebo, 22.8%)
  - The median time to initiation of open-label tafamidis was 17.2 months and the median duration of exposure to tafamidis was 11.4 months (acoramidis, 11.6 months; placebo, 10.5 months)[7]

METHODS

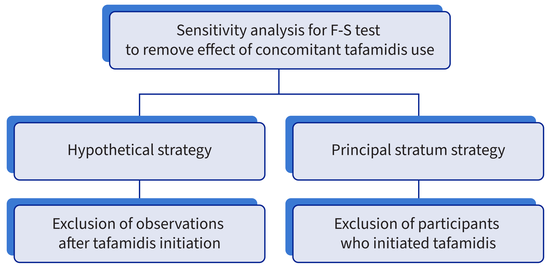
- Two sensitivity analyses were conducted on the primary hierarchical efficacy endpoint.
- The primary efficacy analysis was conducted using the Finkelstein-Schoenfeld (F-S) test, which compares pairs of study participants by prioritized sequence (**Figure 1**)
- We used a standard approach to estimate the effect of acoramidis, assuming that tafamidis was not used
- The primary analysis was conducted in the mITT population without considering the use of concomitant tafamidis in participants
- The sensitivity analyses (F-S test) were conducted to address the potential effect of concomitant tafamidis treatment: one removing the observations after tafamidis initiation (hypothetical strategy) and one removing the participants who initiated tafamidis (principal stratum strategy; **Figure 2**)

FIGURE 1: F-S Scoring Algorithm for the Four-Step Primary Hierarchical Analysis



In pairwise comparisons of NT-proBNP levels at a given visit, a win is declared if the difference in CFB values in NT-proBNP between two study participants is ≥ 500 pg/mL (if so, the participant with the smaller CFB in NT-proBNP wins); if the difference in CFB values between the two participants is < 500 pg/mL, the comparison would be considered a tie. In pairwise comparisons of 6MWD at a given visit, the participant with the greater positive CFB value wins; if the two participants have the same CFB values, the comparison would be considered a tie. The paired comparison for NT-proBNP levels and 6MWD uses the last available nonmissing pair for both participants. A score is assigned with the following rules: win = 1, tie = 0, loss = −1.

FIGURE 2: Prespecified Sensitivity Analyses



RESULTS

- Baseline demographics and characteristics were generally well balanced between treatment groups (**Table**)
- The proportion of participants who received concomitant tafamidis in the acoramidis group was lower than in the placebo group (14.9% [61/409] versus 22.8% [46/202], respectively; **Table**)

TABLE: Baseline Demographics and Characteristics; mITT Population (N = 611)

Demographic/Characteristic	Acoramidis (n = 409)	Acoramidis Without Tafamidis (n = 348)	Placebo (n = 202)	Placebo Without Tafamidis (n = 156)
Age, years, mean (SD)	77.3 (6.47)	77.3 (6.59)	77.0 (6.74)	77.2 (6.68)
Sex, n (%)				
Male	374 (91.4)	319 (91.7)	181 (89.6)	141 (90.4)
Female	35 (8.6)	29 (8.3)	21 (10.4)	15 (9.6)
TTR genotype, n (%)[a]				
Wild type	370 (90.5)	313 (89.9)	182 (90.1)	140 (89.7)
Variant	39 (9.5)	35 (10.1)	20 (9.9)	16 (10.3)
NYHA functional class, n (%)				
I	51 (12.5)	38 (10.9)	17 (8.4)	11 (7.1)
II	288 (70.4)	252 (72.4)	156 (77.2)	120 (76.9)
III	70 (17.1)	58 (16.7)	29 (14.4)	25 (16.0)
NT-proBNP, pg/mL, median (IQR)	2273.0 (1315.0–3872.0)	2325.5 (1327.0–3764.5)	2273.5 (1128.0–3590.0)	2251.0 (1013.5–3800.5)
eGFR, mL/min/1.73 m^2, mean (SD)	62.0 (17.35)	61.4 (17.18)	62.5 (17.53)	62.1 (18.08)
Serum TTR, mg/dL, mean (SD)	23.0 (5.58)	23.0 (5.75)	23.6 (6.08)	23.8 (6.11)
Participants who received concomitant tafamidis, n (%)	61 (14.9)	NA	46 (22.8)	NA

[a]Genetic status as recorded in the interactive voice/web response system at randomization.

- For the primary hierarchical efficacy endpoint, the prespecified hypothetical and principal stratum strategy analyses were both highly statistically significant, which is consistent with the primary analysis (all $p < 0.0001$; **Figure 3**)

FIGURE 3: F-S Primary Analysis With Hypothetical Strategy and With Principal Stratum Strategy; mITT Population (N = 611)

F-S Analysis for Hierarchical Combination of ACM, CVH, CFB in NT-proBNP, and CFB in 6MWD

	Primary Analysis		With Hypothetical Strategy		With Principal Stratum Strategy	
	Acoramidis (n = 409)	Placebo (n = 202)	Acoramidis (n = 409)	Placebo (n = 202)	Acoramidis (n = 348)	Placebo (n = 156)
Participants with ACM at Month 30, n (%)	79 (19.3)	52 (25.7)	75 (18.3)	42 (20.8)	75 (21.6)	42 (26.9)
CVH in participants without ACM at Month 30 (per year), mean (SD)	0.132 (0.3257)	0.293 (0.5751)	0.136 (0.4019)	0.322 (0.6179)	0.137 (0.3350)	0.301 (0.6133)
	Ties		**Ties**		**Ties**	
Mortality — ACM		71.9%		77.3%		70.1%
Morbidity — Cumulative frequency of CVH		44.9%		51.1%		44.1%
Morbidity — CFB in NT-proBNP		14.7%		18.3%		15.2%
Function — CFB in 6MWD		0.4%		1.0%		0.5%
		***p* < 0.0001**		***p* < 0.0001**		***p* < 0.0001**

CONCLUSIONS

- **In ATTRibute-CM, the results of the two prespecified sensitivity analyses pertaining to the concomitant use of tafamidis were consistent with results from the primary efficacy analysis**
- **Concomitant use of tafamidis in ATTRibute-CM did not impact the efficacy results observed with acoramidis**

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ABBREVIATIONS: 6MWD, 6-minute walk distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CFB, change from baseline; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; F-S, Finkelstein-Schoenfeld; IQR, interquartile range; mITT, modified intention-to-treat; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; TTR, transthyretin.

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