Acoramidis-Mediated Early Increase in Serum Transthyretin is Associated With Lower Cardiovascular-Related Hospitalizations and Mortality: Insights From the ATTRibute-CM Study

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OBJECTIVE

- **To evaluate the association between acoramidis-mediated early increases in serum transthyretin (sTTR) levels and first cardiovascular-related hospitalization (CVH) and cardiovascular-related mortality (CVM) in participants with transthyretin amyloid cardiomyopathy (ATTR-CM) in the phase 3 ATTRibute-CM study (NCT03860935)**

BACKGROUND

- ATTR-CM is a progressive disease characterized by destabilization of transthyretin (TTR), leading to progressive heart failure, significantly impaired quality of life, hospitalizations, and death[1–3]
- Patients with ATTR-CM may have lower circulating sTTR levels (a measure of TTR stabilization), which have been shown to be associated with greater mortality[4,5]
- 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 CVH and reduce cardiovascular death. Acoramidis is also approved in Europe for the treatment of wild-type or variant ATTR-CM in adults[6–9]
- In a pivotal phase 3 ATTRibute-CM study, treatment with acoramidis resulted in a rapid (by Day 28) and sustained increase in sTTR levels, as well as 50% and 30% relative risk reductions in the annual frequency of CVH and CVM, respectively[9,10]

METHODS

- The study design of ATTRibute-CM has been described previously[9]
  - Briefly, participants with ATTR-CM were randomized 2:1 to receive acoramidis HCl (800 mg) or matching placebo twice daily for 30 months
  - 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
- sTTR concentrations were determined at baseline, on Day 28, and every 3 months thereafter until Month 30 using a standardized clinical assay for serum prealbumin (sTTR) performed in a central laboratory. The change from baseline (CFB) in mean sTTR levels (mg/dL) for the various visits until Month 30 were analyzed
- CVH was defined as a nonelective admission to an acute care setting for cardiovascular-related morbidity that resulted in a stay of ≥ 24 hours. CVH included events of clinical interest, which were unplanned medical visits of < 24 hours requiring treatment with an intravenous diuretic for the management of decompensated heart failure
- CVM included death adjudicated as cardiovascular or of undetermined cause by the clinical events committee, cardiac mechanical assist device implantation, or heart transplantation
- The association between CFB at Day 28 in sTTR levels and CVH and CVM was analyzed using a stratified Cox proportional hazards model
  - Only those participants in the mITT population who did not experience any events and were not censored through Day 28 were used for this analysis; events refer to either CVH or CVM events for each analysis set

CONCLUSIONS

- **Acoramidis treatment achieves rapid and near-complete TTR stabilization, which results in early and substantial increases in serum TTR by Day 28 that are associated with significant reductions in the risks of CVM and CVH by Month 30 in patients with ATTR-CM**

RESULTS

Baseline Demographics and Characteristics

- Baseline demographics and characteristics of participants were well balanced between the acoramidis and placebo arms (**Table**)

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

Demographic/Characteristic	Acoramidis (n = 409)	Placebo (n = 202)
Age, years, mean (SD)	77.3 (6.47)	77.0 (6.74)
Sex, n (%)		
Male	374 (91.4)	181 (89.6)
Female	35 (8.6)	21 (10.4)
TTR genotype, n (%)[a]		
Wild type	370 (90.5)	182 (90.1)
Variant	39 (9.5)	20 (9.9)
NYHA functional class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
NT-proBNP, pg/mL, median (IQR)	2273.0 (1315.0–3872.0)	2273.5 (1128.0–3590.0)
eGFR, mL/min/1.73 m^2, mean (SD)	62.0 (17.35)	62.5 (17.53)
sTTR, mg/dL[b]		
Mean (SD)	23.0 (5.58)	23.6 (6.08)
Median (IQR)	23.0 (20.0–27.0)	23.0 (20.0–28.0)

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

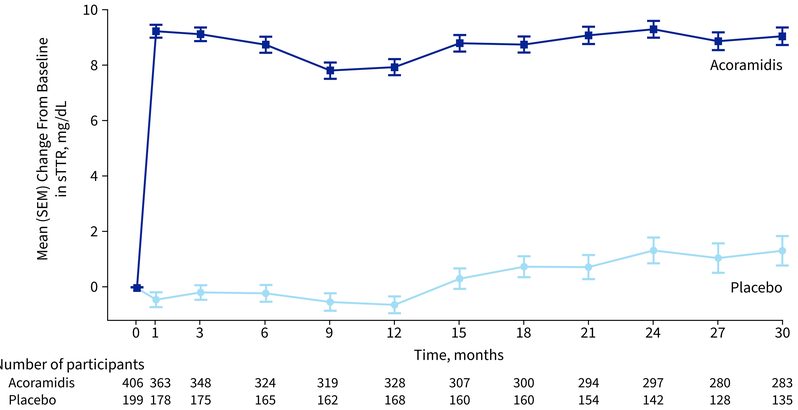
Change From Baseline in sTTR Levels

- Acoramidis treatment resulted in a greater increase in sTTR levels at Day 28 (mean [standard error of the mean (SEM)] CFB: 9.2 [0.25] mg/dL) compared with placebo (mean [SEM] CFB: –0.4 [0.29] mg/dL) and remained stable through Month 30 (**Figure 1**)

Correlation Analyses Between sTTR Levels and Clinical Endpoints of First CVH and CVM (in participants who did not experience any events and were not censored through Day 28)

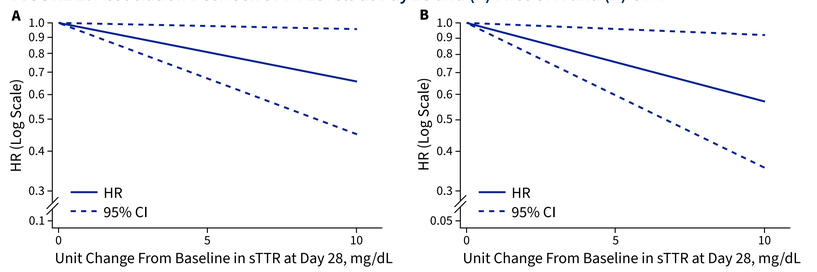
- CVH was reported in 95/360 (26.4%) participants in the acoramidis arm and 71/175 (40.6%) participants in the placebo arm
  - The Cox proportional hazards model analysis for CVH demonstrated that CFB increases in sTTR at Day 28 of 1, 5, and 10 mg/dL post-therapeutic intervention resulted in hazard ratios (HRs) of 0.959, 0.810, and 0.656, respectively (**Figure 2A**)
- CVM was reported in 53/363 (14.6%) participants in the acoramidis arm and 38/178 (21.3%) participants in the placebo arm
  - The CFB in sTTR levels at Day 28 post-therapeutic intervention showed that early increases in sTTR levels of 1, 5, and 10 mg/dL, resulted in HRs of 0.945, 0.755, and 0.569, respectively (**Figure 2B**)

FIGURE 1: Change From Baseline in Mean sTTR Levels of Participants Receiving Acoramidis or Placebo; mITT Population (N = 611)



Number of participants												
Acoramidis	406	363	348	324	319	328	307	300	294	297	280	283
Placebo	199	178	175	165	162	168	160	160	154	142	128	135

FIGURE 2: Association Between sTTR Levels at Day 28 and (A) First CVH and (B) CVM



HR (95% CI) for CVH associated with sTTR change from baseline at Day 28 (p = 0.0283)[a]			
sTTR change from baseline at Day 28	1 mg/dL	5 mg/dL	10 mg/dL
HR (95% CI)	0.959 (0.923–0.996)	0.810 (0.671–0.978)	0.656 (0.450–0.956)
Risk reduction, %	4.1	19.0	34.4

HR (95% CI) for CVM associated with sTTR change from baseline at Day 28 (p = 0.0213)[b]			
sTTR change from baseline at Day 28	1 mg/dL	5 mg/dL	10 mg/dL
HR (95% CI)	0.945 (0.901–0.992)	0.755 (0.594–0.959)	0.569 (0.352–0.919)
Risk reduction, %	5.5	24.5	43.1

The model included baseline 6-minute walk distance and CFB to Day 28 in sTTR levels as covariates and was stratified by treatment group and randomization stratification factors of genotype, NT-proBNP levels (≤ 3000 vs > 3000 pg/mL), eGFR (≥ 45 vs < 45 mL/min/1.73 m^2) as recorded in the interactive voice/web response system, and baseline sTTR levels (≥ 20 vs < 20 mg/dL).
[a]Only those participants in the mITT population with Day 28 CFB in sTTR levels who did not experience any CVH events and were not censored (acoramidis, n = 360; placebo, n = 175). [b]Only those participants in the mITT population with Day 28 CFB in sTTR levels who did not experience any CVM events and were not censored (acoramidis, n = 363; placebo, n = 178).

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ABBREVIATIONS: ATTR-CM, transthyretin amyloid cardiomyopathy; CFB, change from baseline; CI, confidence interval; CVH, cardiovascular-related hospitalization; CVM, cardiovascular-related mortality; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IQR, interquartile range; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; SEM, standard error of the mean; sTTR, serum transthyretin; TTR, transthyretin.

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