Acoramidis Increases Serum TTR Levels in Patients With Wild-Type or Variant Transthyretin Amyloid Cardiomyopathy

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OBJECTIVE

- **To investigate the effect of acoramidis on serum transthyretin (sTTR) levels and clinical outcomes in participants with either wild-type transthyretin amyloid cardiomyopathy (ATTRwt-CM) or variant ATTR-CM (ATTRv-CM) in the phase 3 ATTRibute-CM trial (NCT03860935)**

BACKGROUND

- ATTR-CM is a progressive disease characterized by destabilization of transthyretin (TTR) and aggregation of amyloid fibrils in the heart, leading to progressive heart failure, significantly impaired quality of life, hospitalizations, and death[1–3]
- The destabilization of TTR can occur due to age-related factors (ATTRwt-CM) or due to mutations in the *TTR* gene, which produce pathogenic TTR variants (ATTRv-CM)[1,4]
- Patients with ATTRv-CM typically have lower levels of sTTR and an earlier disease onset, followed by a more rapid clinical progression than patients with ATTRwt-CM because variant TTR-containing tetramers are less stable and more prone to dissociation than wild-type TTR tetramers[3,5,6]
- 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 ATTRwt-CM or ATTRv-CM in adults to reduce cardiovascular death and cardiovascular-related hospitalization (CVH). Acoramidis is also approved in Europe for the treatment of ATTRwt-CM or ATTRv-CM in adults[7–9]
- In a phase 2 study of participants with ATTR-CM, acoramidis treatment resulted in sTTR level increases from baseline to within the normal range for participants with ATTRwt-CM and for those with ATTRv-CM[7]
- In the phase 3 ATTRibute-CM study in participants with ATTR-CM, acoramidis treatment led to a 36% and 42% risk reduction in the composite of all-cause mortality (ACM) or first CVH and ACM or recurring CVH, respectively, versus placebo.[8,10] Acoramidis treatment further resulted in a rapid increase in sTTR levels (by Day 28), which were sustained through Month 30[11]

METHODS

- The study design of ATTRibute-CM has been described previously[11]
  - 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[11]
  - 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
- Participants were permitted to initiate concomitant open-label tafamidis treatment at any time from Month 12 onwards, at the discretion of the investigator
  - In the mITT population, 14.9% of participants in the acoramidis group and 22.8% of participants in the placebo group received concomitant tafamidis at any time during the trial[11]
  - The median times to tafamidis initiation in the acoramidis and placebo groups were 17.8 and 16.1 months, respectively[11]
  - The median durations of exposure to tafamidis were 11.6 and 10.5 months for the acoramidis and placebo groups, respectively[11]
- The genetic status of participants was recorded in the interactive voice/web response system at randomization
- sTTR concentrations were determined at baseline, on Day 28, and then every 3 months until Month 30 using a standardized clinical assay for serum prealbumin (sTTR) performed in a central laboratory
- Time-to-event analyses for ACM or first CVH were performed using a stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6-minute walk distance as a covariate, and was stratified by the randomization factors of genotype, levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and eGFR, as recorded in the interactive voice/web response system at randomization

CONCLUSIONS

- **In the ATTRibute-CM study, acoramidis treatment, a near-complete TTR stabilizer, led to an increase in serum TTR and clinical outcome benefits at Month 30 in both the ATTRwt-CM and ATTRv-CM subgroups:**
  - **sTTR levels at baseline were lower in participants with ATTRv-CM than in those with ATTRwt-CM**
  - **Acoramidis treatment induced a greater proportional increase from baseline in sTTR levels in participants with ATTRv-CM than in those with ATTRwt-CM, resulting in similar absolute sTTR levels achieved at Day 28 and Month 30, thereby providing comparable levels of TTR stabilization**
- **The sTTR level increase with acoramidis was accompanied by a significant reduction in the risk of ACM or first CVH versus placebo in both the ATTRwt-CM (31.2% risk reduction) and ATTRv-CM (59.1% risk reduction) subgroups**
- **Given the higher risk posed by ATTRv-CM, these results are of particular clinical relevance in meeting the distinct medical needs of the variant patient population**

RESULTS

Baseline Demographics and Characteristics

- In ATTRibute-CM, in the mITT population at randomization, 552 participants were identified as having ATTRwt-CM (acoramidis, n = 370; placebo, n = 182) and 59 participants were identified as having ATTRv-CM (acoramidis, n = 39; placebo, n = 20; **Table**)
- The most common TTR variants were p.V142I, p.I88L, and p.T80A (**Table**)
- Baseline demographics and characteristics were generally balanced between the groups across genotypes and treatments (**Table**)
- Mean (SD) baseline sTTR levels were lower in the ATTRv-CM subgroup (acoramidis, 17.8 [5.12] mg/dL; placebo, 17.2 [5.22] mg/dL) than in the ATTRwt-CM subgroup (acoramidis, 23.6 [5.34] mg/dL; placebo, 24.3 [5.75] mg/dL; **Table**)

TABLE: Baseline Demographics and Characteristics by ATTR-CM Genotype; mITT population (N = 611)

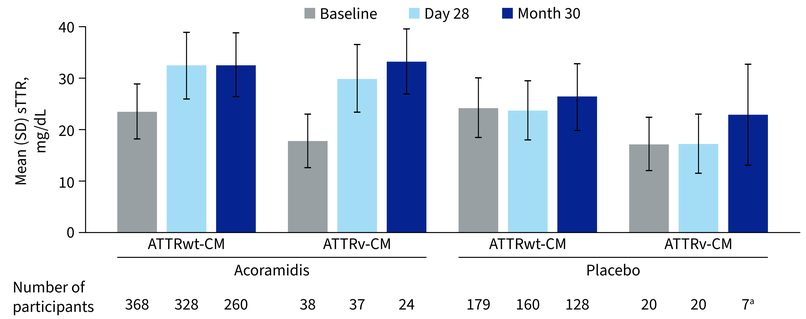
Demographic/Characteristic	Acoramidis (n = 409)		Placebo (n = 202)	
	ATTRwt-CM (n = 370)	ATTRv-CM (n = 39)	ATTRwt-CM (n = 182)	ATTRv-CM (n = 20)
Age, years, mean (SD)	77.7 (6.25)	73.9 (7.60)	77.6 (6.32)	71.2 (7.84)
Sex, n (%)				
Male	341 (92.2)	33 (84.6)	167 (91.8)	14 (70.0)
Female	29 (7.8)	6 (15.4)	15 (8.2)	6 (30.0)
Most common TTR variants, n/N (%)[a]				
p.V142I	NA	23/37 (62.2)	NA	12/19 (63.2)
p.I88L	NA	4/37 (10.8)	NA	3/19 (15.8)
p.T80A	NA	3/37 (8.1)	NA	2/19 (10.5)
NT-proBNP, pg/mL, mean (SD)	2874.8 (2169.84)	2775.4 (1971.32)	2634.9 (1897.14)	2788.8 (1964.70)
NYHA functional class, n (%)				
Class I	49 (13.2)	2 (5.1)	16 (8.8)	1 (5.0)
Class II	253 (68.4)	35 (89.7)	140 (76.9)	16 (80.0)
Class III	68 (18.4)	2 (5.1)	26 (14.3)	3 (15.0)
sTTR, mg/dL				
Mean (SD)	23.6 (5.34)	17.8 (5.12)	24.3 (5.75)	17.2 (5.22)
Median (IQR)	23.0 (20.0–27.0)	19.0 (13.0–21.0)	24.0 (21.0–28.0)	18.0 (12.5–20.0)

[a]In total, 59/611 participants were categorized as having ATTRv-CM at randomization; subsequently, mutations were identified in the clinical database in 56/611 participants.

sTTR Levels

- At Day 28, sTTR levels increased from baseline with acoramidis treatment in both the ATTRwt-CM and ATTRv-CM subgroups; these increases were sustained through Month 30 (**Figure 1**)
  - Acoramidis treatment resulted in a greater mean (SD) increase from baseline in sTTR levels in participants with ATTRv-CM than in those with ATTRwt-CM at Day 28 (12.42 [6.708] mg/dL versus 8.87 [4.402] mg/dL) and Month 30 (14.33 [6.098] mg/dL versus 8.56 [5.445] mg/dL), resulting in similar sTTR levels in both groups at Month 30
- In the placebo ATTRwt-CM and ATTRv-CM subgroups, sTTR levels were similar at baseline and Day 28, and a modest increase in sTTR levels was observed at Month 30 (**Figure 1**)

FIGURE 1: Mean sTTR Levels by ATTR-CM Genotype; mITT population (N = 611)

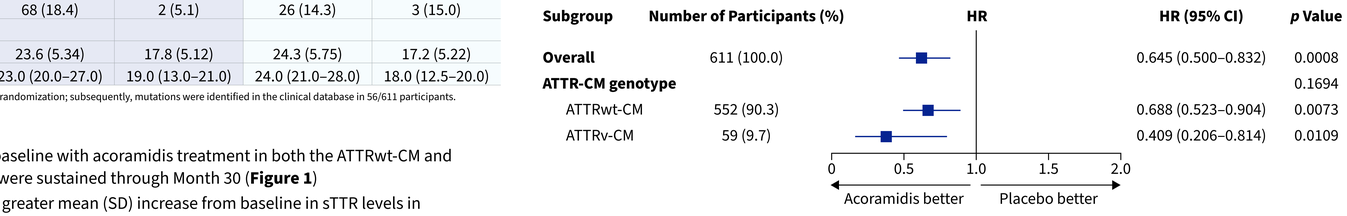


[a]Among the seven ATTRv-CM participants in the placebo group who completed the Month 30 visit, two participants received concomitant tafamidis treatment after Month 12. In the five participants who received placebo treatment only and who completed the Month 30 visit, the mean (SD) sTTR was 18.4 (3.32) mg/dL at baseline and 19.0 (4.20) mg/dL at Month 30.

Time-to-Event Analysis of ACM or First CVH

- Overall, participants in the acoramidis group had a 35.5% lower risk of ACM or first CVH than those in the placebo group (hazard ratio [HR], 0.645 [95% confidence interval (CI): 0.500–0.832], $p = 0.0008$; **Figure 2**)
- Acoramidis treatment was associated with a significantly lower risk of ACM or first CVH than placebo in both the ATTRwt-CM subgroup (risk reduction, 31.2%; HR, 0.688 [95% CI: 0.523–0.904], $p = 0.0073$) and the ATTRv-CM subgroup (risk reduction, 59.1%; HR, 0.409 [95% CI: 0.206–0.814], $p = 0.0109$; **Figure 2**)

FIGURE 2: HR of ACM or First CVH by ATTR-CM Genotype; mITT population (N = 611)



ACM was defined as death from any cause, heart transplantation, and implantation of a durable cardiac mechanical assist device in participants with end-stage heart failure. CVH was defined as a nonelective admission to an acute care setting for cardiovascular-related morbidity that resulted in a ≥ 24-hour stay, or an unscheduled medical visit of < 24 hours for the purpose of intravenous diuretic therapy to manage decompensated heart failure. ACM and CVH events were reviewed and adjudicated by an independent clinical events committee blinded to treatment.

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ABBREVIATIONS: ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; CVH, cardiovascular-related hospitalization; 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; sTTR, serum transthyretin; TTR, transthyretin.

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