# Effect of Acoramidis on All-Cause Mortality, Cardiovascular Hospitalization, and NT-proBNP in Variant ATTR-CM: Results From ATTRibute-CM

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## PURPOSE

- **To assess the efficacy of acoramidis on the composite of all-cause mortality (ACM) and cardiovascular-related hospitalization (CVH), and the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the subgroup of participants from ATTRibute-CM with variant transthyretin amyloid cardiomyopathy (ATTRv-CM)**

## BACKGROUND

- Transthyretin amyloid cardiomyopathy (ATTR-CM), characterized by the destabilization of transthyretin (TTR), can occur owing to age-related factors (wild-type ATTR-CM [ATTRwt-CM]) or inherited mutations in the *TTR* gene, which produce pathogenic TTR variants (ATTRv-CM)[1,2]
- Acoramidis, a highly selective, oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in Europe, the USA, and Japan for the treatment of ATTRwt-CM and ATTRv-CM in adults[3–6]
- In the phase 3 ATTRibute-CM study (NCT03860935) in participants with ATTR-CM,[7] acoramidis treatment was associated with a 42% risk reduction in ACM or recurrent CVH ($p = 0.0005$), a 50% risk reduction in the annual frequency of CVH ($p < 0.0001$), and a lower increase in NT-proBNP at Month 30, compared with placebo[8]

## METHODS

- The ATTRibute-CM study design has been described previously[7]
- Efficacy outcomes were assessed in the ATTRv-CM subgroup of the modified intention-to-treat (mITT) population, which consisted of all randomized participants who received at least one dose of acoramidis or placebo, had at least one post-baseline efficacy evaluation, and had a baseline estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m$^2$
- ACM included death owing to any cause, heart transplant, or implantation of a cardiac mechanical assist device (commonly known as a ventricular assist device)
- CVH included cardiovascular hospitalizations (≥ 24 hours) and urgent outpatient visits (< 24 hours) for decompensated heart failure requiring intravenous diuretics
  - CVH events were adjudicated by an independent Clinical Events Committee blinded to treatment
- Time-to-event analyses were performed using a stratified Cox proportional hazards model that included treatment, baseline 6-minute walk distance, genotype, and genotype x treatment interaction, and was stratified by the randomization factors of NT-proBNP level and eGFR as recorded at randomization
- Adjusted geometric mean fold change from baseline in NT-proBNP level was analysed using the mixed effects model with repeated measures after log transformation
  - The model included treatment group, visit, genotype, eGFR, treatment group-by-visit, genotype-by-treatment group, genotype-by-visit, and genotype-by-treatment group-by-visit as factors, and the baseline value as a covariate. Genotype and eGFR were based on information from the IXRS at randomization

## CONCLUSIONS

- **In participants with ATTRv-CM in the ATTRibute-CM study, acoramidis treatment for 30 months led to a substantial reduction (> 50%) in the composite of ACM or first CVH, ACM, and first CVH, compared with placebo**
  - **This improvement was accompanied by a significant mitigation of the rise in NT-proBNP levels from baseline to Month 30 observed with placebo**
- **These improvements in participants with ATTRv-CM are consistent with and also of greater magnitude than the results of the overall mITT population from ATTRibute-CM[7,8]**
  - **Furthermore, they are consistent with the greater increase from baseline to Month 30 in serum TTR levels observed with acoramidis treatment in participants with ATTRv-CM than with acoramidis treatment in participants with ATTRwt-CM in this study[9]**
- **Acoramidis, a near-complete TTR stabilizer, may be a meaningful option for the more aggressive underlying disease in patients with ATTRv-CM**

## RESULTS

- In total, 59 participants (9.7% [59/611]) in the ATTRibute-CM mITT population were categorized as having ATTRv-CM at randomization (acoramidis, n = 39; placebo, n = 20; **Table 1**)
- At baseline, the two treatment subgroups had similar mean NT-proBNP levels (**Table 1**)
- The three most common TTR variants represented were p.V142I (n = 35), p.I88L (n = 7), and p.T80A (n = 5; **Table 2**)

**TABLE 1: Baseline Demographics and Characteristics in Participants With ATTRv-CM; mITT Population (n = 59)[a]**

| Demographic/Characteristic | Acoramidis (n = 39) | Placebo (n = 20) |
|---|---|---|
| **Age, years, mean (SD)** | 73.9 (7.60) | 71.2 (7.84) |
| **Sex, n (%)** | | |
| Male | 33 (84.6) | 14 (70.0) |
| Female | 6 (15.4) | 6 (30.0) |
| **NYHA functional class, n (%)** | | |
| I | 2 (5.1) | 1 (5.0) |
| II | 35 (89.7) | 16 (80.0) |
| III | 2 (5.1) | 3 (15.0) |
| **NT-proBNP, pg/mL, mean (SD)** | 2775.4 (1971.3) | 2788.8 (1964.7) |

[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.

**TABLE 2: Most Common TTR Variants; mITT Population (n = 56)[a]**

| TTR Variant Genotype, n (%) | Acoramidis (n = 37) | Placebo (n = 19) |
|---|---|---|
| p.V142I | 23 (62.2) | 12 (63.2) |
| p.I88L | 4 (10.8) | 3 (15.8) |
| p.T80A | 3 (8.1) | 2 (10.5) |

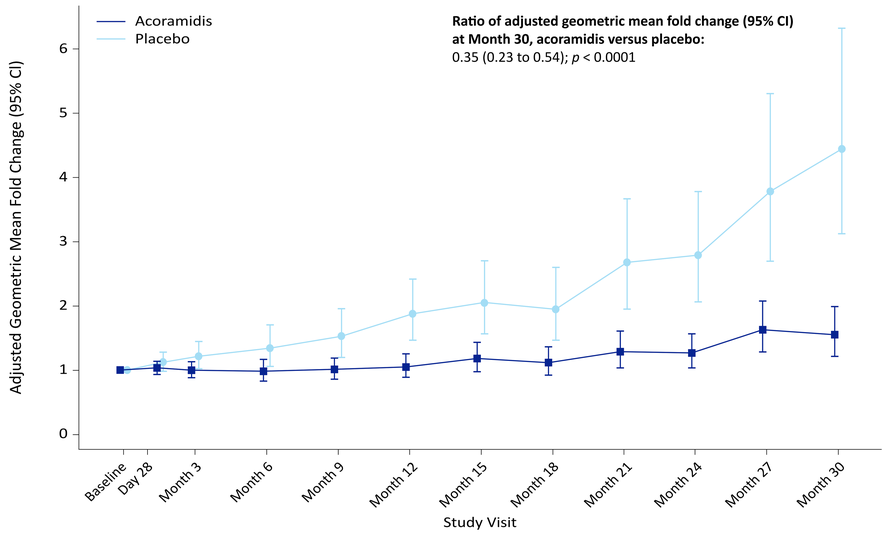
[a]In total, 59/611 participants were categorized as having ATTRv-CM at randomization; subsequently, mutations were identified in the clinical database in 56/611 participants.

- At Month 30, acoramidis treatment reduced the risk of ACM or first CVH (hazard ratio [HR], 0.41; $p = 0.0109$), ACM (HR, 0.45; $p = 0.0619$), and first CVH (HR, 0.35; $p = 0.0058$; **Table 3**) versus placebo
- At Month 30, participants who received acoramidis had a lower adjusted geometric mean fold change from baseline in NT-proBNP than those who received placebo (ratio of adjusted geometric mean fold change: 0.35 [95% CI, 0.23 to 0.54]; $p < 0.0001$; **Figure**)

**TABLE 3: Outcomes at Month 30 in Participants With ATTRv-CM; mITT Population (n = 59)**

| Clinical Event | Acoramidis (n = 39) Relative to Placebo (n = 20) |
|---|---|
| ACM or first CVH, HR (95% CI) | 0.41 (0.21 to 0.81)<br>$p = 0.0109$ |
| ACM, HR (95% CI) | 0.45 (0.20 to 1.04)<br>$p = 0.0619$ |
| First CVH, HR (95% CI) | 0.35 (0.17 to 0.74)<br>$p = 0.0058$ |

**FIGURE: Adjusted Geometric Mean Fold Change From Baseline in NT-proBNP Levels in Participants With ATTRv-CM; mITT Population (n = 59)**

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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; CI, confidence interval; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IXRS, interactive voice/web response system; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; TTR, transthyretin.

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