Acoramidis Has a Beneficial Effect Compared With Placebo on Change From Baseline in NAC ATTR Stage at Month 30 in Patients with ATTR-CM: Results From the ATTRibute-CM Study

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PURPOSE

- **To evaluate the ability of acoramidis to stabilize or improve National Amyloidosis Centre (NAC) stage after 30 months compared with placebo in participants with transthyretin amyloid cardiomyopathy (ATTR-CM) from the phase 3 ATTRibute-CM study (NCT03860935)**

BACKGROUND

- ATTR-CM is a progressive disease characterized by destabilization of transthyretin (TTR), which misfolds, causing the aggregation of amyloid fibrils in the heart.[1–3] This leads to progressive heart failure, impaired quality of life, hospitalizations, and often death[2–4]
- The NAC staging system for ATTR-CM is used to classify patients into prognostic categories based on N-terminal pro-B-type natriuretic peptide (NT-proBNP) level and estimated glomerular filtration rate (eGFR) and predicts ongoing survival throughout the course of ATTR-CM, with survival progressively decreasing from stage I to stage III[5]
- Acoramidis, an oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in the USA, Europe, Japan, and the UK for the treatment of wild-type or variant ATTR-CM in adults[6–10]
- In the phase 3 ATTRibute-CM study, acoramidis was well tolerated and led to a 42% relative risk reduction in the composite of all-cause mortality and recurrent cardiovascular hospitalizations over 30 months compared with placebo ($p = 0.0005$)[11,12]

METHODS

- The ATTRibute-CM study design has been described previously[11]
- Participants with wild-type or variant ATTR-CM aged 18–90 years 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 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 eGFR ≥ 30 mL/min/1.73 m^2
- NAC stage was assessed at baseline and at Month 30
- NAC stages were determined based on NT-proBNP levels and eGFR (**Table**)

TABLE: NAC ATTR Disease Staging Criteria[5]

NAC ATTR Stage	Criteria
Stage I	NT-proBNP level ≤ 3000 pg/mL and eGFR ≥ 45 mL/min/1.73 m^2
Stage II	NT-proBNP level ≤ 3000 pg/mL and eGFR < 45 mL/min/1.73 m^2 or NT-proBNP level > 3000 pg/mL and eGFR ≥ 45 mL/min/1.73 m^2
Stage III	NT-proBNP level > 3000 pg/mL and eGFR < 45 mL/min/1.73 m^2

- Changes in NAC stage from baseline to Month 30 were categorized as "stable", "improved", or "worsened or missing"
  - The "stable" category comprised participants who stayed within the same NAC stage at baseline and at Month 30
  - The "improved" category comprised participants who moved from a higher NAC stage at baseline to a lower stage at Month 30
  - The "worsened or missing" category comprised participants who moved from a lower NAC stage at baseline to a higher stage at Month 30 and participants whose Month 30 NAC stage was missing
- The change in NAC stage was compared between treatment groups using a stratified Cochran-Mantel-Haenszel test with stratification factors of genotype, NT-proBNP level, and eGFR as recorded at randomization

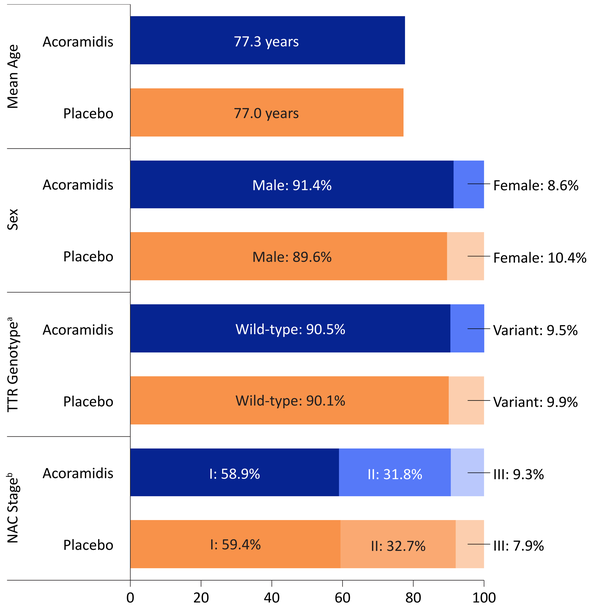
CONCLUSIONS

- Acoramidis treatment resulted in a greater proportion of participants having an improved or stable NAC stage at Month 30 compared with placebo, indicating better stabilization of their disease

RESULTS

- Baseline demographics and clinical characteristics were comparable between treatment groups (**Figure 1**)[12]
  - Most participants had NAC stage I at baseline (acoramidis: 58.9%; placebo: 59.4%)

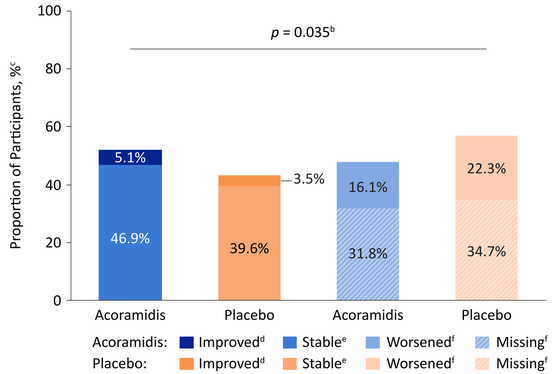
FIGURE 1: Baseline Demographics and Clinical Characteristics by Treatment Group; mITT Population (N = 611; Acoramidis, n = 409; Placebo, n = 202)[12]



[a]TTR genotype was reported at randomization.
[b]Baseline NAC stage is the last assessment obtained before or on the date of the first dose of study drug.

- At Month 30, NAC stage remained stable or improved in 52.1% (213/409) of acoramidis participants compared with 43.1% (87/202) of placebo participants
- NAC stage was worsened in 16.1% of acoramidis participants compared with 22.3% of placebo participants; 31.8% had missing data in the acoramidis group and 34.7% in the placebo group
- The difference between acoramidis and placebo was statistically significant in favour of acoramidis ($p = 0.035$; **Figure 2**)

FIGURE 2: Proportion of Participants with ATTR-CM in ATTRibute-CM With Improved, Stable, or Worsened NAC Stages at Month 30, Relative to Baseline[a]; mITT Population (N = 611; Acoramidis, n = 409; Placebo, n = 202)



[a]Baseline NAC stage is the last assessment obtained before or on the date of the first dose of study drug.
[b]*p* value for acoramidis versus placebo is based on a stratified Cochran-Mantel-Haenszel test with stratification factors of genotype, NT-proBNP level, and eGFR as recorded in the interactive voice/web response system at randomization.
[c]Values are rounded to one decimal place. Totals may not equal the sum of individual categories due to rounding.
[d]The "improved" category comprises patients who moved from a higher NAC stage at baseline to a lower NAC stage at Month 30.
[e]The "stable" category comprises patients who stayed within the same NAC stage at baseline and Month 30.
[f]The "worsened or missing" category comprises patients who moved from a lower NAC stage at baseline to a higher NAC stage at Month 30, and patients whose Month 30 NAC stage was missing for any reason, including death.

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ABBREVIATIONS: ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; mITT, modified intention-to-treat; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTR, transthyretin.

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