Acoramidis Stabilizes or Improves NYHA Class at Month 30 to a Greater Extent Than Placebo in Patients With ATTR-CM: Results From the ATTRibute-CM Study

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OBJECTIVE

- **To assess the treatment effect of acoramidis on New York Heart Association (NYHA) functional class 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 the destabilization of transthyretin (TTR) and aggregation of amyloid fibrils in the heart, leading to progressive heart failure, a 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 wild-type or variant ATTR-CM in adults to reduce cardiovascular death and cardiovascular-related hospitalization. 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, acoramidis improved clinical outcomes in participants with ATTR-CM compared with placebo and was well tolerated[7]
- The NYHA four-stage classification is a subjective, clinical assessment that characterizes symptoms and functional status in patients with heart failure (HF; **Table 1**)[8]
- NYHA Class is an independent predictor of mortality in patients with ATTR-CM and provides incremental value to existing ATTR-CM risk scores[9]
  - Patients in NYHA Class III/IV are known to have a worse prognosis than patients with Class I/II[10]
- Improvement from baseline in NYHA Class is associated with reduced risks of cardiovascular-related mortality and hospitalization; conversely, worsening in NYHA Class is associated with increased risks of these outcomes[11]

TABLE 1: NYHA Classes and Corresponding Functional Status

NYHA Class	Functional Status
Class I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
Class IV	Unable to perform any physical activity without symptoms of HF and symptoms of HF at rest

METHODS

- The study design of ATTRibute-CM has been described previously[7]
- Briefly, participants with ATTR-CM aged 18–90 years with NYHA Class I–III 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
- NYHA Class at baseline and change from baseline at Month 30 was reported
  - Baseline NYHA Class was the last assessment obtained before or on the date of the first dose of the study drug
- NYHA Classes I and II were combined into one category and NYHA Classes III and IV were combined into another category
- Changes from baseline to Month 30 in NYHA Class were measured and categorized as:
  - "improved": participants who moved from Class III to Class I/II
  - "stable": participants who stayed within Class I/II or Class III/IV
  - "worsened": participants who moved from Class I/II to Class III/IV. Study participants who died or had missing NYHA assessments at Month 30 were conservatively categorized as having "worsened" in NYHA Class
- The difference (common risk difference), 95% confidence interval (CI), and *p* values were calculated using a stratified Cochran-Mantel-Haenszel test with stratification factors of genotype, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, and eGFR at randomization

CONCLUSIONS

- **Acoramidis treatment resulted in a greater proportion of participants whose NYHA Class was stable or improved at Month 30 compared with placebo**
- **These favorable findings on clinician-assessed symptoms and functional class are consistent with previously reported results from ATTRibute-CM demonstrating reduced disease progression[7]**

RESULTS

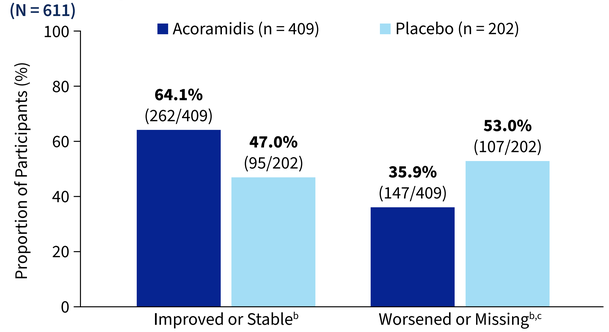
- Baseline demographics and characteristics of the 611 participants in the mITT population were generally well balanced between the treatment groups (**Table 2**)
- Most participants had NYHA Class I/II at baseline (acoramidis, 82.9%; placebo, 85.6%). No participants had NYHA Class IV at baseline
- At Month 30, NYHA Class improved or remained stable in 64.1% of participants in the acoramidis group compared with 47.0% of participants in the placebo group (difference: 17.2%; $p < 0.0001$; **Figure**)
  - A change from NYHA Class III to Class I/II was observed in 19 of 70 (27.1%) participants in the acoramidis group and 3 of 29 (10.3%) participants in the placebo group
  - Of the participants who remained stable in the NYHA Class III group, 23 of 70 (32.9%) participants in the acoramidis group and 11 of 29 (37.9%) participants in the placebo group remained in Class III, and two participants in the acoramidis group and no participants in the placebo group moved from Class III to Class IV
- At Month 30, 35.9% of participants in the acoramidis group and 53.0% of participants in the placebo group had worsened in NYHA Class or had missing values (**Figure**)
  - A change from Class I/II to Class III/IV was observed in 27 (8.0%) participants in the acoramidis group and 40 (23.1%) participants in the placebo group

TABLE 2: Baseline Demographics and Characteristics; 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 (%)[b]		
Class I/II[c]	339 (82.9)	173 (85.6)
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
Class III/IV[c]	70 (17.1)	29 (14.4)
III	70 (17.1)	29 (14.4)
IV	0	0
NT-proBNP, pg/mL		
Mean (SD)	2865.3 (2149.64)	2650.1 (1899.48)
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)
Serum TTR, mg/dL, mean (SD)	23.0 (5.58)	23.6 (6.08)

[a]Genetic status as recorded in the interactive voice/web response system at randomization. [b]Participants with NYHA Classes I–III were eligible to participate in the study, whereas participants with Class IV were not eligible to enter the study. [c]NYHA Classes I and II are combined into one category and NYHA Classes III and IV are combined into another category.

FIGURE: Change From Baseline to Month 30 in NYHA Class[a]; mITT Population (N = 611)



	Change From Baseline to Month 30 in NYHA Class, n (%)[a]		Common Risk Difference (95% CI)[d]	*p* Value[d]
	Acoramidis (n = 409)	Placebo (n = 202)		
Improved or stable[b]	262 (64.1)	95 (47.0)	17.2% (9.2, 25.2)	**< 0.0001**
Worsened or missing[b,c]	147 (35.9)	107 (53.0)	–17.2% (–25.2, –9.2)	

[a]NYHA Classes I and II are combined into one category and NYHA Classes III and IV are combined into another category. [b]Number of participants with missing NYHA Class at baseline: 0. Number of participants with missing NYHA Class at Month 30: acoramidis = 120; placebo = 67. [c]Participants who died or had missing NYHA assessments at Month 30 were conservatively categorized as having "worsened". [d]The difference (common risk difference), 95% CI, and *p* value are based on a stratified Cochran-Mantel-Haenszel test with stratification factors of genotype, NT-proBNP level, and eGFR at randomization.

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ABBREVIATIONS: ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; 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; TTR, transthyretin.

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