Consistent Benefit on Kansas City Cardiomyopathy Questionnaire Overall Summary Score With Acoramidis Treatment Compared With Placebo Across Participant Subgroups in ATTRibute-CM

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PURPOSE

- **To evaluate the effect of acoramidis on heart failure-related health status as assessed by the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score across participant subgroups from the ATTRibute-CM study (NCT03860935)**

BACKGROUND

- Transthyretin amyloid cardiomyopathy (ATTR-CM), an infiltrative, restrictive, life-threatening, and progressive disease caused by destabilized transthyretin (TTR) tetramers, is associated with impaired health status (symptoms, function, and quality of life)[1–3]
- The KCCQ measures a patient's perspective of their heart failure-related health status[4]
- Acoramidis, an oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in the USA, the European Union, Japan, the UK, and Switzerland for the treatment of adults with ATTR-CM[5–10]
- In the phase 3 ATTRibute-CM study, acoramidis treatment markedly attenuated the decline in KCCQ-OS score through Month 30 compared with placebo (least-squares mean difference: 9.9 points; 95% confidence interval [CI]: 5.97–13.91; $p < 0.0001$)[11]
- The consistency of this benefit across clinically relevant patient subgroups has not been fully characterized

METHODS

- The ATTRibute-CM study design has been described previously[11]
  - Briefly, eligible adult participants (≤ 90 years old) were randomized 2:1 to receive acoramidis HCl 800 mg or placebo twice daily for 30 months; concomitant tafamidis use was permitted after Month 12 at the discretion of the investigator
- Efficacy analyses were conducted in the modified intention-to-treat (mITT) population, defined as all randomized participants who received at least one dose of acoramidis or placebo, had at least one post-baseline efficacy assessment, and had a baseline estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m²
- At Month 30, the least-squares mean change from baseline difference between treatment groups in KCCQ-OS score was estimated using a mixed effects model for repeated measures
- A pre-specified sensitivity analysis was performed, which excluded all participants who received concomitant tafamidis at any time during the study
- Efficacy analyses at Month 30 were performed in the following pre-specified subgroups: ATTR-CM genotype (wild-type vs variant), N-terminal pro-B-type natriuretic peptide (NT-proBNP; ≤ 3000 vs > 3000 pg/mL), eGFR (≥ 45 vs < 45 mL/min/1.73 m²), age (< 78 vs ≥ 78 years), country (USA vs rest of world), and New York Heart Association (NYHA) functional class (I/II vs III)

Limitations: The ATTRibute-CM study population had a relatively low proportion of some subgroups (e.g. women, African American individuals, participants with variant ATTR-CM), which may have affected the health status outcomes reported here

CONCLUSIONS

- **Acoramidis treatment significantly attenuated the decline in heart failure-related health status compared with placebo in participants with ATTR-CM**
- **This treatment effect was observed consistently across all pre-specified participant subgroups, including those with variant ATTR-CM and those with advanced heart failure symptoms, suggesting that acoramidis treatment confers health status benefits relative to placebo across the ATTR-CM disease spectrum**

RESULTS

- Baseline demographics and characteristics were generally well balanced between the treatment groups (**Table 1**)

TABLE 1: Baseline Demographics and Characteristics; mITT Population (N = 611)

	Acoramidis (n = 409)	Placebo (n = 202)
Age, years, mean (SD)	77.3 (6.5)	77.0 (6.7)
Sex, male, n (%)	374 (91.4)	181 (89.6)
Wild-type ATTR-CM,[a] n (%)	370 (90.5)	182 (90.1)
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)
6MWD,[b] m, mean (SD)	362.8 (103.5)	351.5 (93.8)
eGFR, mL/min/1.73 m², mean (SD)	62.0 (17.4)	62.5 (17.5)
NT-proBNP, pg/mL, median (Q1–Q3)	2273 (1315–3872)	2274 (1128–3590)
Serum TTR,[c] mg/dL, mean (SD)	23.0 (5.6)	23.6 (6.1)
KCCQ-OS score,[d] mean (SD)	71.7 (19.4)	70.5 (20.7)

[a]TTR genotype was reported at randomization. [b]Acoramidis, n = 407. [c]Acoramidis, n = 406; placebo, n = 199. [d]Acoramidis, n = 408.

- The sensitivity analysis, excluding participants who received concomitant tafamidis, demonstrated a clinically meaningful benefit favouring treatment with acoramidis alone at Month 30 versus placebo (least-squares mean difference between treatment groups: 9.7 points [95% CI: 5.26–14.13]; $p < 0.0001$; **Table 2**)

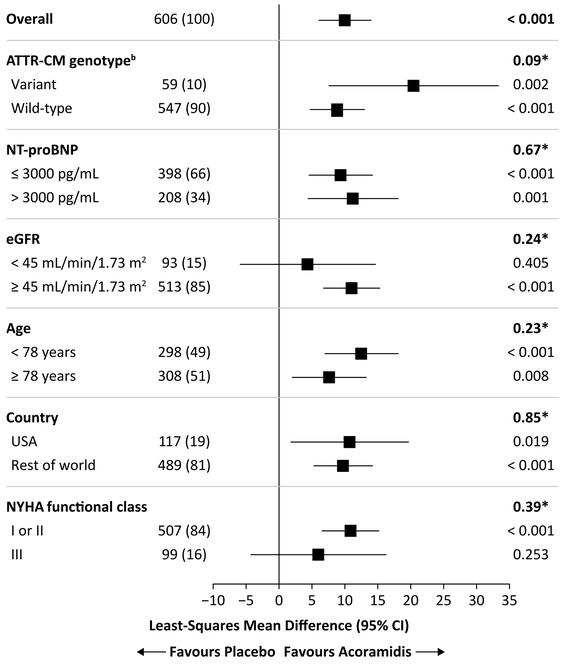
TABLE 2: Change From Baseline in KCCQ-OS Score Through Month 30 in the mITT Population (N = 611) and in the Sensitivity Analysis Excluding Concomitant Tafamidis (n = 504)

	mITT Population		Sensitivity Analysis	
	Acoramidis (n = 409)	Placebo (n = 202)	Acoramidis (n = 348)	Placebo (n = 156)
Baseline (observed values)				
n	408	202	347	156
Mean (SD)	71.7 (19.4)	70.5 (20.7)	71.3 (19.5)	68.9 (21.8)
Month 30 (change from baseline)				
n	405	201	345	155
Least-squares mean (SE)	−11.5 (1.18)	−21.4 (1.65)	−12.9 (1.27)	−22.6 (1.88)
Least-squares mean difference (SE)[a]	9.9 (2.02)		9.7 (2.26)	
95% CI	5.97–13.91		5.26–14.13	
p value	< 0.0001		< 0.0001	

[a]Difference expressed as acoramidis – placebo.
The mixed effects model for repeated measures analysis included treatment group, visit, ATTR-CM genotype (wild-type vs variant), NT-proBNP concentration (≤ 3000 vs > 3000 pg/mL), eGFR (≥ 45 vs < 45 mL/min/1.73 m²), and the treatment group-by-visit interaction as factors, and baseline KCCQ-OS score as a covariate. Randomization stratification factors of ATTR-CM genotype, NT-proBNP, and eGFR were based on information from the interactive voice/web response system.

- The benefit of acoramidis on KCCQ-OS score through Month 30 was observed across all pre-specified participant subgroups versus placebo, with no evidence of treatment-effect heterogeneity (**Figure 1**)
  - *p* values were significant (< 0.05) in each participant subgroup except for eGFR < 45 mL/min/1.73 m² and NYHA functional class III, which both favoured acoramidis over placebo but were limited by small participant numbers

FIGURE 1: Forest Plot for the Change From Baseline in KCCQ-OS Score Through Month 30 Overall and by Participant Subgroup for Acoramidis Compared With Placebo; mITT Population (N = 611)



p values indicated with * are from testing the interaction of the subgroup and treatment; other *p* values are from testing the treatment difference at the given value of the subgroup variable.
[a]Data are from participants with available values. [b]TTR genotype was reported at randomization.

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