Effect of Acoramidis on Functional Capacity and Quality of Life in Patients With Variant ATTR-CM: Results From ATTRibute-CM

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PURPOSE

- **To assess the treatment effect of acoramidis on functional capacity and health-related quality of life (QoL) in the subgroup of participants from ATTRibute-CM (NCT03860935) 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]
- Patients with ATTRv-CM typically have an earlier disease onset followed by a more rapid clinical progression than patients with ATTRwt-CM[3]
- 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[4–7]
- In the phase 3 ATTRibute-CM study, acoramidis improved clinical outcomes, functional capacity (assessed by 6-minute walk distance [6MWD]), and health-related QoL (assessed by the Kansas City Cardiomyopathy Questionnaire overall summary [KCCQ-OS] score) compared with placebo, and was well tolerated in participants with ATTR-CM[8]
  - The decline in 6MWD at Month 30 was significantly less in the acoramidis group than in the placebo group (LS mean difference: 39.6 m [95% CI, 21.1 to 58.2]; $p < 0.001$). In addition, a higher proportion of participants experienced an improvement in 6MWD (net increase from baseline to Month 30) with acoramidis (26%) than with placebo (13%)[a,b]
  - The decline in KCCQ-OS score at Month 30 was significantly less in the acoramidis group than in the placebo group (LS mean difference: 9.9 points [95% CI, 6.0 to 13.9]; $p < 0.001$). Additionally, a higher proportion of participants experienced an improvement in KCCQ-OS score with acoramidis (31%) than with placebo (18%)[a,c]
- A difference of 35 m in 6MWD or 5 points in KCCQ-OS score has been reported as being clinically meaningful[9,10]

METHODS

- The ATTRibute-CM study design has been described previously[8]
- 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
- The changes from baseline in 6MWD and in KCCQ-OS score were analysed using mixed-effects models with repeated measures. These models included treatment group, visit, genotype, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, eGFR level, treatment group-by-visit, genotype-by-treatment group, genotype-by-visit, and genotype-by-treatment group-by-visit as factors, and baseline 6MWD or KCCQ-OS score as covariates. Genotype, NT-proBNP level, 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 demonstrated a statistically significant and clinically meaningful improvement in functional capacity (6MWD: +87 m) and health-related QoL (KCCQ-OS score: +20 points), relative to 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 the ATTRibute-CM study[8]**
- **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 a comparable mean 6MWD and mean KCCQ-OS score (**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)
6MWD, m, mean (SD)	364.6 (94.93)	354.7 (97.07)
KCCQ-OS score, mean (SD)	68.5 (17.20)	63.2 (24.74)

[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.

- Acoramidis treatment demonstrated a significant and clinically meaningful treatment benefit on 6MWD at Month 30 compared with placebo (LS mean difference: 86.7 m; nominal p value = 0.0048; **Figure 1**)
- Acoramidis treatment demonstrated a significant and clinically meaningful treatment benefit on KCCQ-OS score at Month 30 compared with placebo (LS mean difference: 20.3 points; nominal p value = 0.0019; **Figure 2**)

FIGURE 1: Change From Baseline in 6MWD in Participants with ATTRv-CM; mITT Population (n = 59)

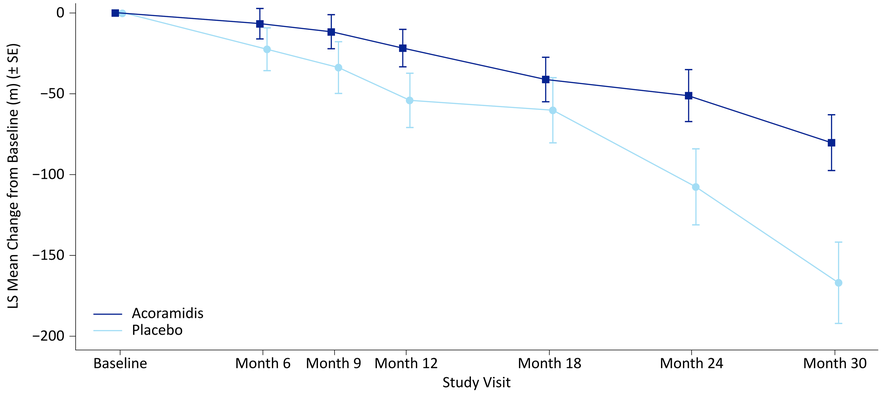
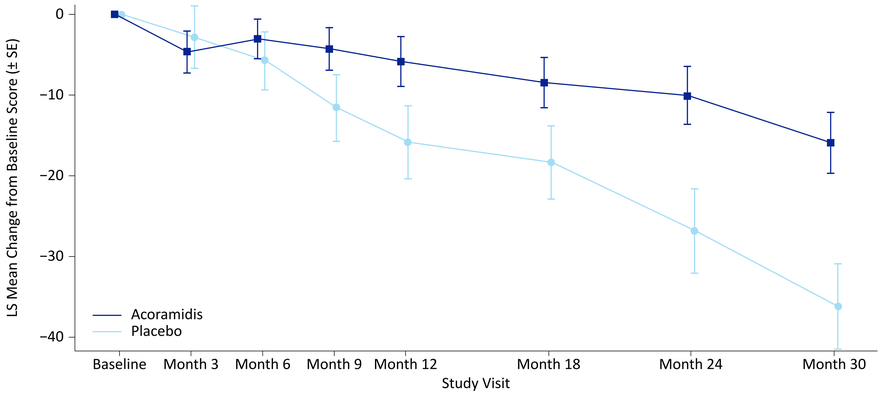


FIGURE 2: Change From Baseline in KCCQ-OS Score in Participants With ATTRv-CM; mITT Population (n = 59)



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ABBREVIATIONS: 6MWD, 6-minute walk distance; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; IXRS, interactive voice/web response system; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire overall summary; LS, least-squares; m, metres; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life; SD, standard deviation; SE, standard error; TTR, transthyretin.

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[a]Missing values at baseline or Month 30 were imputed as not meeting the definition of net increase.
[b]The observed percentages of participants who had improved 6MWD (and who were assessed at both baseline and Month 30) were 40% with acoramidis and 22% with placebo.
[c]The observed percentages of participants who had an improved KCCQ-OS score (and who were assessed at both baseline and Month 30) were 44% with acoramidis and 27% with placebo.

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