Effect of Acoramidis on Improvement or Maintenance of Heart Failure-Related Health Status as Assessed by Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) Score in ATTRibute-CM

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PURPOSE

- **To integrate survival and heart failure-related health status, as assessed by the Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS) score, into a single analysis to describe the efficacy of acoramidis on outcomes in participants from the ATTRibute-CM study (NCT03860935)**

BACKGROUND

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is characterized by worsening heart failure, leading to impaired quality of life, hospitalizations, and often death[1,2]
  - — A primary goal in managing ATTR-CM is to slow disease progression to preserve or improve patients' symptoms, function, and quality of life
  - — The KCCQ measures a patient's perspective of their heart failure-related health status[3]
- Acoramidis, an oral transthyretin (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[4–9]
- In the phase 3 ATTRibute-CM study, acoramidis demonstrated a favourable trend toward reduced all-cause mortality (ACM) through Month 30 compared with placebo[10,11]
- Acoramidis also significantly attenuated the decline in KCCQ-OS score through Month 30 (least-squares mean difference: 9.9 points; 95% confidence interval [CI]: 6.0–13.9; $p < 0.001$),[10] and a higher proportion of participants experienced an improvement in KCCQ-OS score (net increase from baseline) with acoramidis (31%) than with placebo (18%)
- Because the analysis of KCCQ-OS score at Month 30 can only be assessed in survivors, an approach integrating death and KCCQ-OS score is needed to better characterize the overall treatment benefit and support clinical decision-making

METHODS

- The ATTRibute-CM study design has been described previously[10]
  - — 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 m^2
- To integrate survival and health status into a single analysis, at Month 30 the effect of acoramidis on KCCQ-OS score was compared with placebo as participants 'alive and not worse', those 'alive and well', and those 'alive and better' (**Table 1**) using a Cochran-Mantel-Haenszel test with stratification factors of TTR genotype (wild-type versus variant), N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, and eGFR; numbers needed to treat (NNTs) with 95% CIs were calculated as the inverse of the absolute risk reductions and their 95% CIs, using the Mantel-Haenszel method
- Participants with a missing change from baseline value for KCCQ-OS score who were alive at Month 30 were excluded from the analysis. Participants who experienced ACM by Month 30 were also excluded

TABLE 1: Definitions of KCCQ-OS Score Outcomes

Outcome	Definition
Alive and not worse (two thresholds examined)	Alive and a decrease from baseline in KCCQ-OS score of either < 5 or < 10 points
Alive and well	Alive and KCCQ-OS score of > 60 with a decrease from baseline of < 10 points
Alive and better (two thresholds examined)	Alive and an increase from baseline in KCCQ-OS score of either > 5 or > 10 points

Limitations: KCCQ-OS scores were analysed only for participants who survived to Month 30, which may have skewed the analyses towards those with better health status

CONCLUSIONS

- **In patients with ATTR-CM, acoramidis treatment was associated with a significantly greater likelihood of survival without worsening heart failure-related health status, and with improved heart failure-related health status compared with placebo**
- **Although not all participants experienced improvement, these findings suggest a clinically meaningful modification of disease trajectory**
- **These data provide an integrated assessment of heart failure-related health status and survival to inform medical decision-making**

RESULTS

- Baseline demographics and characteristics were generally well balanced between the treatment groups (**Table 2**)

TABLE 2: Baseline Demographics and Characteristics; mITT Population (N = 611)

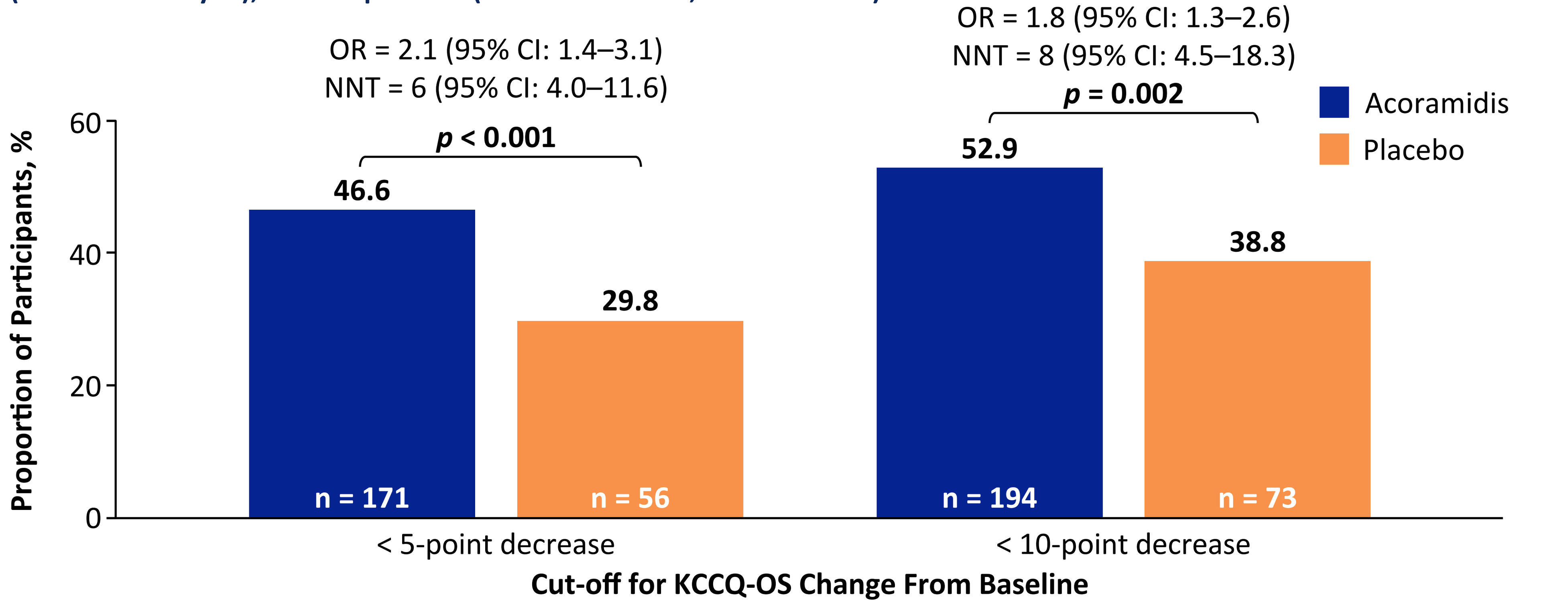
	Acoramidis (n = 409)	Placebo (n = 202)
Age, years, mean (SD)	77.3 (6.5)	77.0 (6.7)
Sex, male, n (%)	374 (91.4)	181 (89.6)
Wild-type ATTR-CM,[a] n (%)	370 (90.5)	182 (90.1)
NYHA functional class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
6MWD,[b] m, mean (SD)	362.8 (103.5)	351.5 (93.8)
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.

Alive and Not Worse

- At Month 30, the proportion of participants who were 'alive and not worse' significantly favoured acoramidis versus placebo (difference: 16.8% using a cut-off of < 5-point decrease; 14.1% using a cut-off of < 10-point decrease; **Figure 1**)

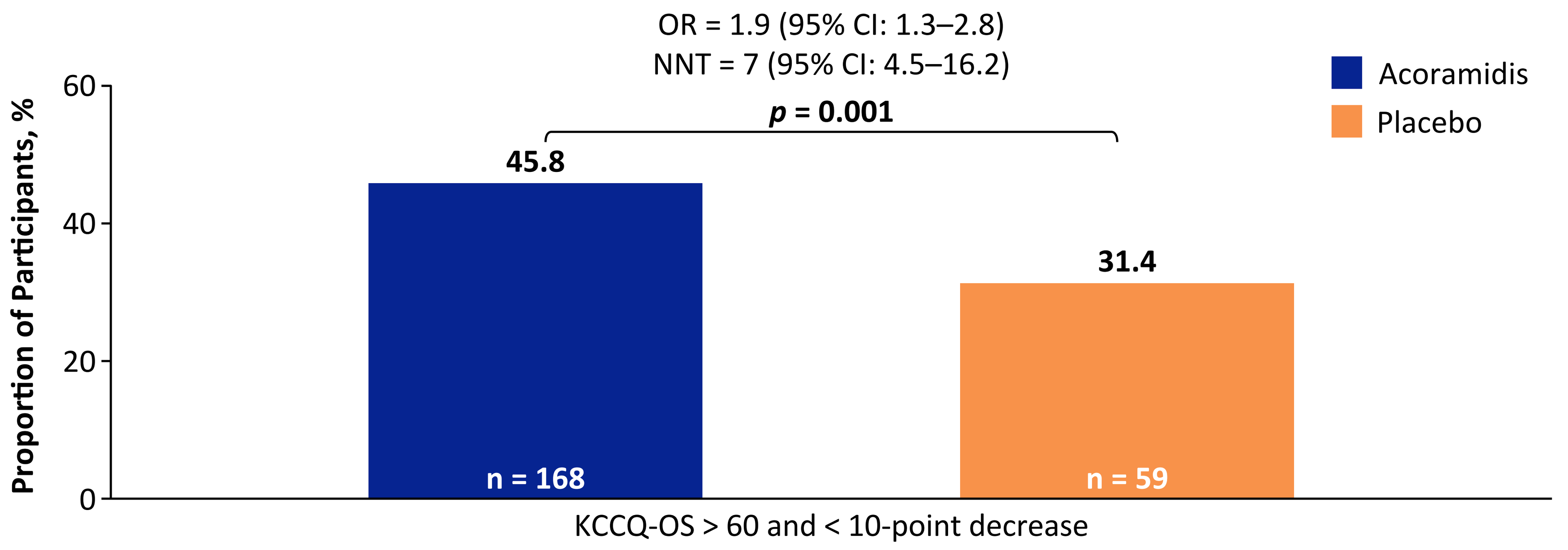
FIGURE 1: Proportions of Participants With Stable or Improved KCCQ-OS Score at Month 30 Who Were Alive and Not Worse (Observed Analysis); mITT Population (Acoramidis = 367; Placebo = 188)



Alive and Well

- At Month 30, more acoramidis recipients were 'alive and well' than placebo recipients (difference: 14.4%; **Figure 2**)

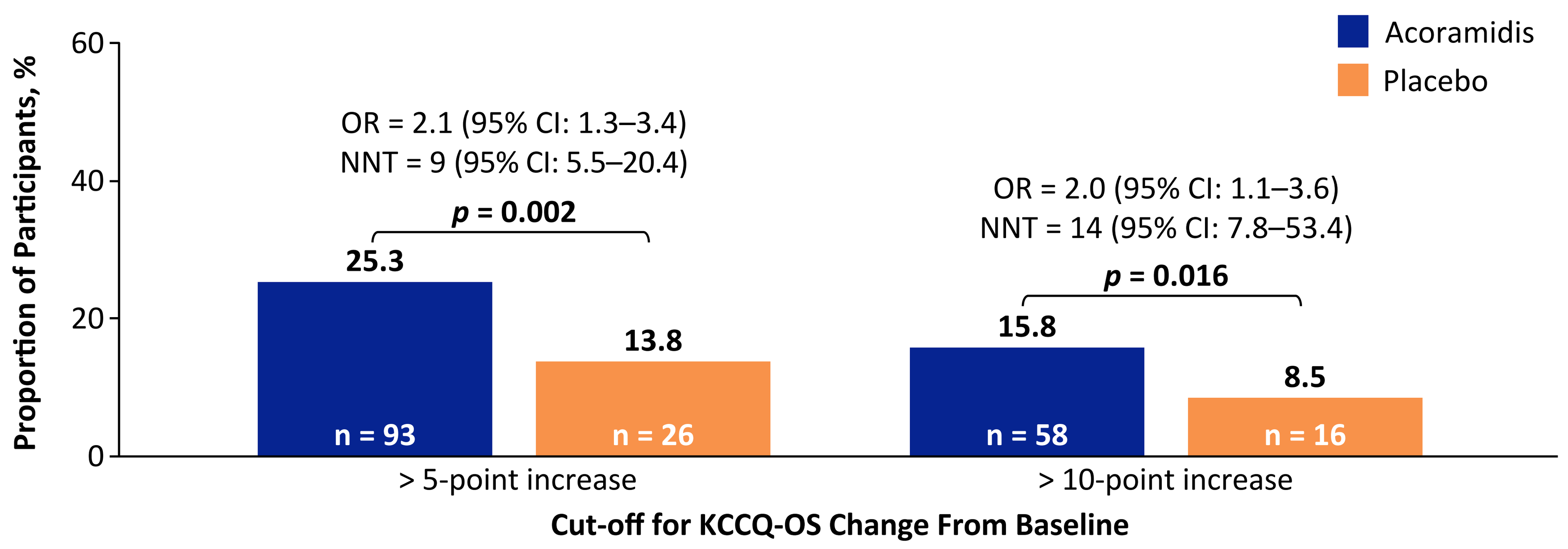
FIGURE 2: Proportions of Participants With Stable or Improved KCCQ-OS Score at Month 30 Who Were Alive and Well (Observed Analysis); mITT Population (Acoramidis = 367; Placebo = 188)



Alive and Better

- At Month 30, the proportion of participants who were 'alive and better' significantly favoured acoramidis versus placebo (difference: 11.5% using a cut-off of > 5-point increase; 7.3% using a moderate > 10-point improvement cut-off; **Figure 3**)

FIGURE 3: Proportions of Participants With Stable or Improved KCCQ-OS Score at Month 30 Who Were Alive and Better (Observed Analysis); mITT Population (Acoramidis = 367; Placebo = 188)



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ABBREVIATIONS: 6MWD, 6-minute walk distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; eGFR, estimated glomerular filtration rate; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; mITT, modified intention-to-treat; NNT, number needed to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; Q1, first quartile; Q3, third quartile; SD, standard deviation; TTR, transthyretin.

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