Acoramidis Reduces Days Lost to Death and/or Cardiovascular-Related Hospitalization, Preserving Time Alive Outside the Hospital in Participants With ATTR-CM: Results From ATTRibute-CM

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PURPOSE

- **To evaluate the effect of acoramidis on reducing days lost to death and/or cardiovascular-related hospitalization (DLDCVH) versus placebo in participants with transthyretin amyloid cardiomyopathy (ATTR-CM) over 30 and 36 months**

CONCLUSIONS

- **In participants with ATTR-CM, acoramidis significantly reduced DLDCVH versus placebo**
- **Acoramidis preserved more than 1 month (38 days) of time alive outside the hospital over 30 months versus placebo, with this benefit extending to 65 days over 36 months using OLE-based data and to 94 days with placebo-extrapolated estimates, reflecting progressive divergence in outcomes over time**
- **A greater proportion of acoramidis-treated participants experienced zero DLDCVH than placebo recipients, consistent with a clinically meaningful treatment benefit with acoramidis**
- **These findings suggest that acoramidis may reduce healthcare resource utilization by decreasing hospitalization burden while helping patients spend more time alive at home, an important consideration for healthcare decision-making**

BACKGROUND

- ATTR-CM results from the destabilization of transthyretin (TTR) tetramers, which leads to progressive, often fatal, heart failure[1,2]
- Acoramidis is an oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization and is approved for the treatment of ATTR-CM in the European Union, Switzerland, the UK, the USA, and other countries[3–9]
- In the phase 3 ATTRibute-CM study, acoramidis reduced the risk of the composite endpoint of all-cause mortality (ACM) or first cardiovascular-related hospitalization (CVH) through Month 30 by 36% versus placebo in participants with ATTR-CM[10]
- DLDCVH is a patient-centred metric that integrates mortality, frequency of CVH, and length of hospital stay into a single measure of disease burden and healthcare resource utilization, with reductions reflecting fewer inpatient bed days and more time alive outside the hospital

METHODS

- The study designs of ATTRibute-CM (NCT03860935) and its open-label extension study (OLE; NCT04988386) have been previously described[11,12]
  - — ATTRibute-CM participants were randomized 2:1 to receive acoramidis HCl 800 mg or matching placebo twice daily for 30 months
  - — Eligible participants were invited to receive open-label acoramidis in the OLE
  - — Open-label tafamidis use was permitted at the discretion of the investigator from Month 12 to Month 30 in ATTRibute-CM; tafamidis use was not permitted in the OLE
- Three post hoc analyses of DLDCVH 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 ≥ 30 mL/min/1.73 m^2
  - — The Month 30 analysis used model-based estimates for participants with 907 days of follow-up, corresponding to the maximum follow-up duration (30 months) in ATTRibute-CM
  - — The Month 36 analyses used ATTRibute-CM + OLE data for all participants (OLE-based analysis), or ATTRibute-CM + OLE data for those randomized to acoramidis and only ATTRibute-CM data for those randomized to placebo (placebo-extrapolated analysis)
- Analyses were based on a zero-inflated beta model that included treatment group, log-transformed follow-up time, and log-transformed baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP), genotype, and estimated glomerular filtration rate at randomization
- ACM was defined as death from any cause or receipt of a heart transplant or an implanted cardiac mechanical assist device
- CVH events were adjudicated by a clinical events committee and included non-elective admission to an acute care setting for cardiovascular-related morbidity (lasting ≥ 24 hours) or an urgent heart failure visit, defined as an outpatient visit to an emergency department or urgent care (lasting < 24 hours) for worsening heart failure requiring intravenous diuretics

RESULTS

- Baseline demographics and characteristics were comparable across 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)
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)

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

- Over 30 months (907 days), the estimated mean DLDCVH was 68.5 days (7.5%) for participants treated with acoramidis and 106.4 days (11.7%) for those who received placebo (**Figure 1A,B**)
  - — Acoramidis treatment led to a mean difference of 38.0 fewer DLDCVH over 30 months versus placebo (95% CI: 10.7–65.3; $p = 0.0065$)
- A greater proportion of acoramidis recipients had zero DLDCVH over 30 months compared with placebo recipients (odds ratio [OR] [95% CI]: 2.02 [1.28–2.77]; $p < 0.0001$; **Figure 1C**)
- Over 36 months (1080 days), the mean DLDCVH in the OLE-based analysis was 97.2 days (9.0%) for participants originally randomized to acoramidis and 162.3 days (15.0%) for those originally randomized to placebo (**Figure 2A,B**)
  - — The mean DLDCVH over this period in the placebo-extrapolated analysis was 97.1 days (9.0%) for acoramidis recipients and 191.0 days (17.7%) for placebo recipients (**Figure 3A,B**)
  - — Acoramidis treatment led to a mean difference of 65.1 fewer DLDCVH in the OLE-based analysis and 94.0 fewer DLDCVH in the placebo-extrapolated analysis over 36 months versus placebo (95% CI: 28.4–101.9, $p = 0.0005$; and 48.0–139.9, $p < 0.0001$, respectively)
- Greater proportions of acoramidis recipients had zero DLDCVH over 36 months compared with placebo recipients in both the OLE-based analysis (OR [95% CI]: 2.57 [1.62–3.53]; $p < 0.0001$; **Figure 2C**) and the placebo-extrapolated analysis (OR [95% CI]: 2.23 [1.36–3.11]; $p < 0.0001$; **Figure 3C**)

FIGURE 1: Month 30 Analysis of DLDCVH; mITT Population (Acoramidis, N = 409; Placebo, N = 202)

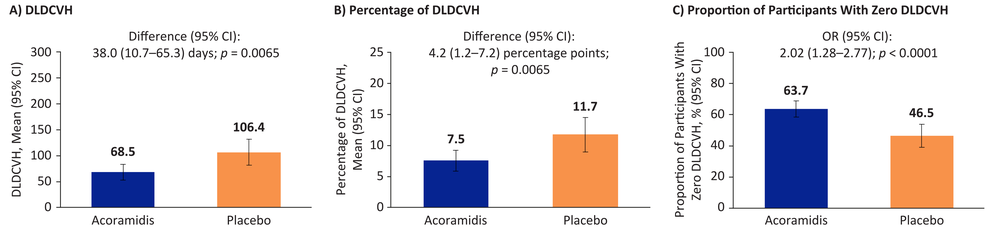
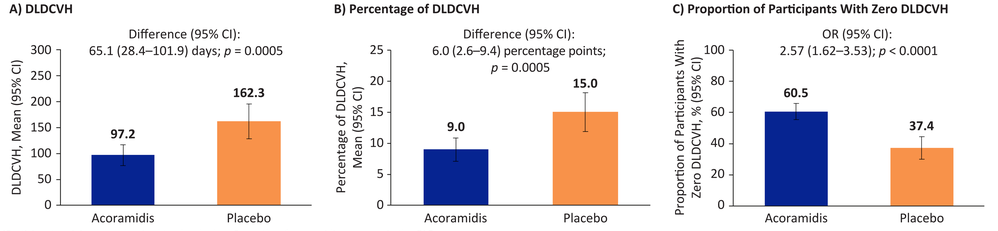
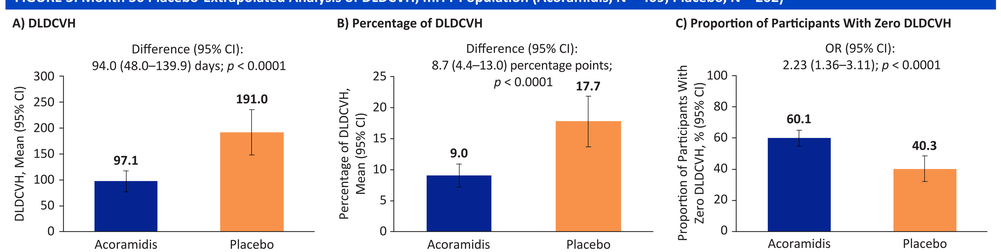


FIGURE 2: Month 36 OLE-Based Analysis of DLDCVH; mITT Population (Acoramidis, N = 409; Placebo,[a] N = 202)



[a]Participants originally randomized to placebo had 6 months of acoramidis exposure in the OLE.

FIGURE 3: Month 36 Placebo-Extrapolated Analysis of DLDCVH; mITT Population (Acoramidis, N = 409; Placebo, N = 202)



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ABBREVIATIONS: 6MWD, 6-minute walk distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; CVH, cardiovascular-related hospitalization; DLDCVH, days lost to death and/or cardiovascular-related hospitalization; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; OR, odds ratio; Q, quartile; SD, standard deviation; TTR, transthyretin.

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