

Clinical Effects of Acoramidis Versus Placebo in the ATTRibute-CM Study: Observations from the Intention-To-Treat Population



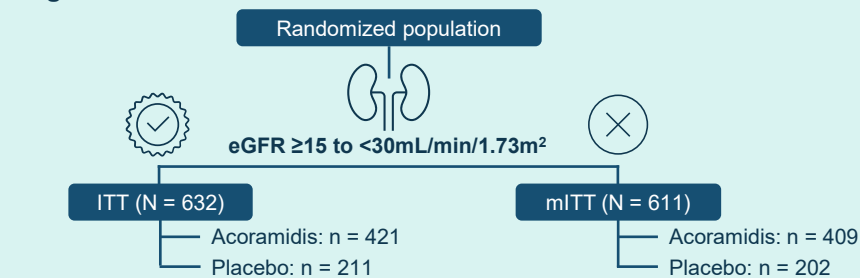
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Background

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive myocardial disease associated with recurrent cardiovascular-related hospitalization (CVH) and death within 3 to 10 years if left untreated.¹
- Acoramidis is an oral transthyretin (TTR) stabilizer that achieves near-complete (≥90%) TTR stabilization,^{2,3} and is approved for the treatment of cardiomyopathy in adults with wild-type or variant ATTR-CM in the US, EU, Japan, and the UK.⁴⁻⁷
- In the pivotal phase 3 ATTRibute-CM study (NCT03860935), acoramidis demonstrated significantly better efficacy versus patient-individualized optimized background therapy in a modified intention-to-treat (mITT) population (N = 611).⁸
- Here, we assess in detail the efficacy and safety of acoramidis versus placebo through 30 months in the ITT population of ATTRibute-CM, which included additional patients with kidney impairment (estimated glomerular filtration rate [eGFR] ≥15 to <30 mL/min/1.73 m²). Differences in study populations are depicted in Figure 1.

Figure 1. mITT versus ITT^a



^aBoth populations comprised patients who had undergone randomization, received at least one dose of acoramidis or placebo and had at least one efficacy evaluation after baseline. The ITT population comprised patients with both preserved and impaired kidney function, whereas the mITT population only included patients with preserved kidney function.
eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; mITT, modified intention-to-treat.

METHODS

- Details of the study design have previously been published.⁸
- Selected clinical and functional outcomes are reported here for data through month 30.
- For the time to event analysis, treatment effect was determined as the hazard ratio (HR) with a 95% confidence interval (CI) derived from a Cox proportional hazards model, incorporating treatment and the baseline value of the 6-minute walk test as covariates (P value calculated using a two-sided log-rank test).
- Relative risk (RR) with 95% CI and two-sided P values were calculated utilizing the Cochran-Mantel-Haenszel test, and stratified by baseline genotype, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and eGFR.
- RR in achieving a ≥5% deterioration and ≥5% improvement in Kansas City Cardiomyopathy Questionnaire—overall summary score (KCCQ-OSS) versus baseline was assessed, with a ≥5-point/≥5% change defining the minimal clinically important difference.⁹⁻¹¹
- For the binary responder analyses (KCCQ), methods for imputing missing values were applied (Jump to Reference [J2R]); in the primary analysis, missing values were imputed and assessed to determine if response threshold was surpassed for the imputed values.
- Annual CVH rate was calculated over the 30-month period as the average number of hospitalizations per patient and the average hospitalizations per patient per year.

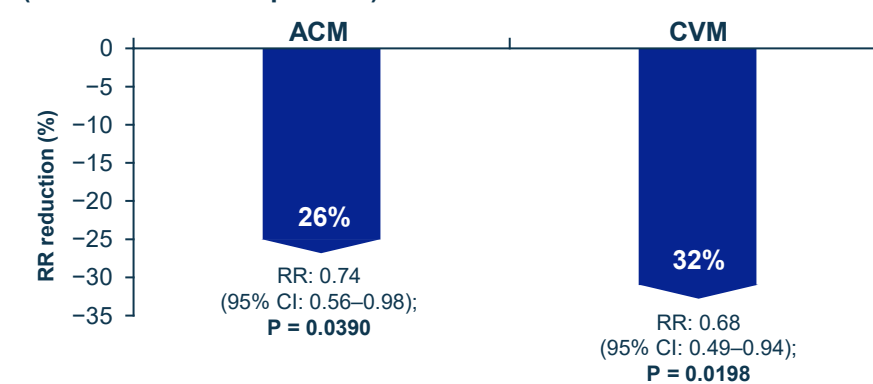
RESULTS

- Baseline demographics and disease characteristics are described in detail elsewhere.⁸

Acoramidis reduced mortality risk versus placebo

- Rates of mortality events were reduced with acoramidis versus placebo:
 - ACM: 19.9% versus 27.0%.
 - CVM: 15.0% versus 22.3%.
- Acoramidis significantly reduced the risk of all-cause mortality (ACM) and cardiovascular mortality (CVM) versus placebo (Figure 2).

Figure 2. RR reduction for mortality outcomes within 30 months (acoramidis versus placebo)

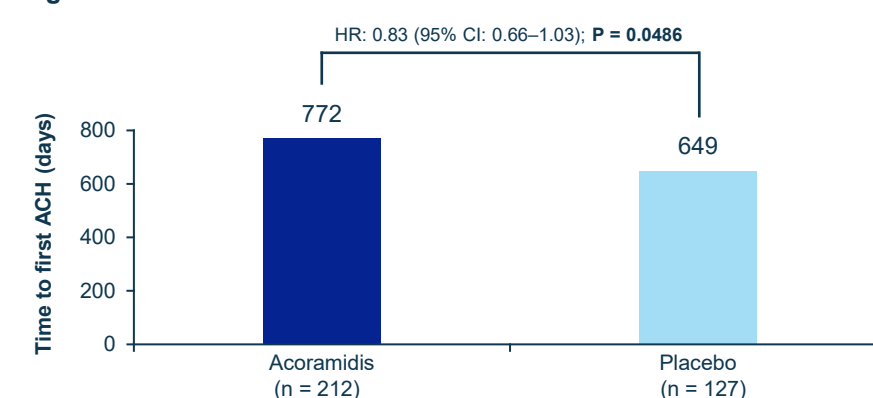


ACM, all-cause mortality; CI, confidence interval; CVM, cardiovascular mortality; RR, relative risk.

Acoramidis improved hospitalization outcomes versus placebo

- First all-cause hospitalization (ACH) occurred approximately 4 months (123 days) later in patients receiving acoramidis (50.4%) versus placebo (60.2%, Figure 3).

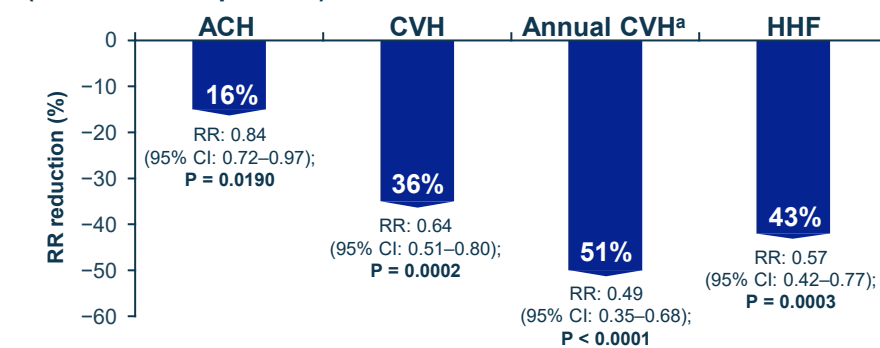
Figure 3. Median time to first ACH



ACH, all-cause hospitalization; CI, confidence interval; HR, hazard ratio.

- Hospitalization outcome rates were reduced with acoramidis versus placebo:
 - ACH: 49.4% versus 59.2%.
 - CVH: 24.9% versus 39.3%.
 - Hospitalization for heart failure (HHF; total): 16.1% versus 28.4%.
- Acoramidis significantly reduced the risk of ACH, CVH, annual CVH, and HHF compared with placebo (Figure 4).

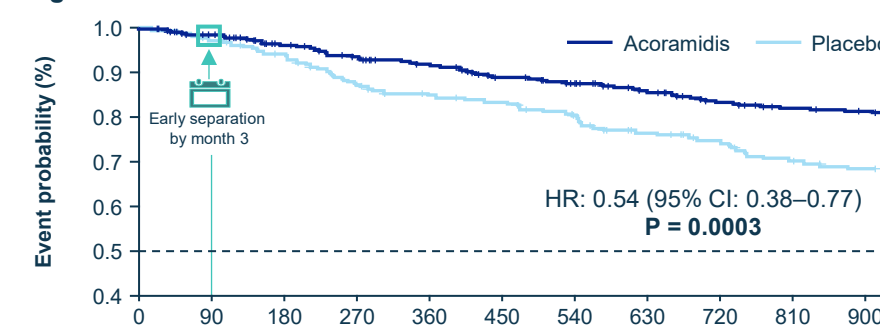
Figure 4. RR reduction^a for hospitalization outcomes (acoramidis vs placebo)



^aData for all outcomes represent RR reduction, except annual CVH, which represents rate risk reduction. ACH, all-cause hospitalization; CI, confidence interval; CVH, cardiovascular-related hospitalization; HHF, hospitalization for heart failure; RR, relative risk.

- Acoramidis reduced probability of first HHF by 46% (Figure 5)

Figure 5. Time to the first HHF

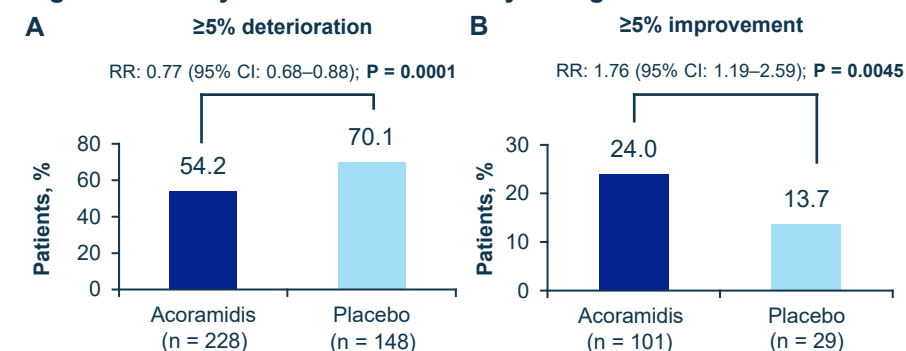


No. at risk:
Acoramidis 421 400 373 356 342 323 314 297 282 270 266
Placebo 211 204 193 177 168 162 152 138 131 122 117
CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio.

Quality of life was maintained or improved with acoramidis

- Significant benefit in the quality of life was observed with acoramidis versus placebo as measured by KCCQ-OSS (Figure 6).

Figure 6. Quality of life as measured by change in KCCQ-OSS



CI, confidence interval; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire—overall summary score; RR, relative risk.

Acoramidis had a favorable safety profile compared with placebo

- Patients treated with acoramidis experienced no significant differences compared with the placebo group regarding any adverse events (AEs), mild AEs, or AEs leading to discontinuation or death.
- A statistically significant reduction in severe and serious (cardiac) AEs versus placebo was observed (Table 1).

Table 1. Overall safety data^a

Patients, n (%)	Acoramidis (n = 421)	Placebo (n = 211)
SAEs	230 (54.6)	137 (64.9)
	RR (95% CI): 0.84 (0.74–0.96); P = 0.0132	
Severe AEs	157 (37.3)	96 (45.5)
	RR (95% CI): 0.82 (0.68–0.99); P = 0.0431	

^aThere were no statistically significant differences in overall rates of AEs. AE, adverse event; CI, confidence interval; RR, relative risk; SAE, serious adverse event.

Consistent effects were observed across subgroups

- Acoramidis led to consistent efficacy and safety results with no subgroup effect modifications for New York Heart Association (NYHA) class, gender, and country.
- Signals were observed for age, genotype, and NT-proBNP, but with no discernible pattern.

CONCLUSIONS

- Our findings reaffirm the efficacy and safety results from the primary mITT analysis of ATTRibute-CM.⁸
- This analysis, which includes all randomized patients, even those with severely reduced kidney function (≥15 to <30 mL/min/1.73 m²), shows sustained benefits of acoramidis treatment on clinical and functional outcomes in all dimensions (mortality, morbidity, quality of life, and safety) through 30 months of treatment.
- Achieving quality of life improvements in this population with a progressive and life-threatening disease is particularly meaningful, as simply limiting disease progression is currently considered treatment success.²
- Consistently positive results were demonstrated across all subgroups, reinforcing the efficacy and safety of acoramidis in all patients with ATTR-CM.

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Conflicts of interest/disclosures

The presenting author, Henrike Charlotte Plate, is an employee of Bayer Vital GmbH.

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