Higher Risk of Mortality in Previously Hospitalized Patients: Insights From ATTRibute-CM

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OBJECTIVE

- **To evaluate the relationship between CVH and subsequent survival across treatment arms in ATTRibute-CM**

INTRODUCTION

- ATTR-CM, caused by the destabilization of the TTR (also known as prealbumin) tetramer, is a chronic disease characterized by progressive heart failure, significantly impaired quality of life, hospitalization, and death[1-3]
- CVH is an indicator of higher mortality in patients with undifferentiated heart failure.[4] Whether this association might be observed in the ATTR-CM population has not been determined
- Acoramidis is a next-generation, investigational, near-complete TTR stabilizer (>90% vs placebo) for the treatment of patients with ATTR-CM[5-7]
- In a phase 3 study (ATTRibute-CM, NCT03860935), acoramidis demonstrated improved clinical outcomes in patients with ATTR-CM, including a 50% reduction in the risk of CVH compared to placebo over 30 months, with a positive treatment effect observed as early as 3 months[7]

METHODS

- Details of the study design have been previously published[7]
- The mITT population (n=611) was the primary analysis population for efficacy endpoints and included randomized participants who received at least 1 dose of study drug and had a baseline eGFR ≥30 mL/min/1.73 m^2
- ACM and cumulative CVH were considered to be the most clinically important components within the primary hierarchical endpoint
  - ACM included CEC-reviewed and -adjudicated death, heart transplant, and implantation of CMAD, defined as a durable CMAD implanted in a participant with end-stage heart failure
  - CVH was defined as a nonelective admission to an acute care setting for cardiovascular-related morbidity that resulted in at least a 24-hour stay (or a date change, if the time of admission/discharge was not available) or an unscheduled medical visit of <24 hours due to heart failure and requiring treatment with IV diuretics
- Kaplan-Meier curves for patients with and without CVH were plotted in this post-hoc analysis

CONCLUSIONS

- **To our knowledge, this is the first time a prospective trial has demonstrated that CVH portends a higher subsequent mortality in patients with ATTR-CM**
- **This suggests that effective treatment to reduce the need for CVH is critically important, and that highly effective, targeted therapy for ATTR-CM that reduces CVH can improve the prognosis of patients with ATTR-CM**

RESULTS

- Demographics and baseline disease characteristics were mostly comparable between patients with and without CVH (**Table**); patients with CVH had higher baseline NT-proBNP and lower eGFR

TABLE. Demographics and Baseline Characteristics by CVH Group (mITT Population)

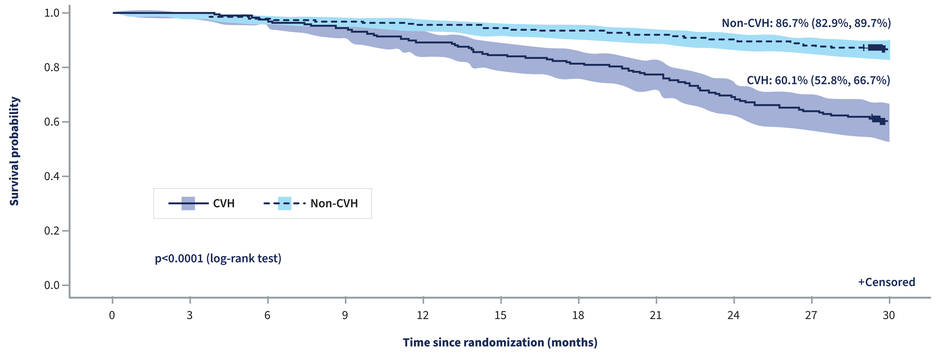
Parameters	Overall Population	
	CVH n=195	Non-CVH n=416
Age, years, mean (SD)	77 (6.3)	77 (6.7)
Male sex, n (%)	174 (89.2)	381 (91.6)
White race/ethnic group, n (%)	176 (90.3)	361 (86.8)
TTR genotype, ATTRwt-CM, n (%)	167 (85.6)	385 (92.5)
NYHA class, n (%) I II III	 12 (6.2) 149 (76.4) 34 (17.4)	 56 (13.5) 295 (70.9) 65 (15.6)
Serum TTR, mg/dL, mean (SD)[a]	23 (6.4)	23 (5.4)
NT-proBNP, ng/L, mean (SD)	3266 (2094.6)	2573 (2025.0)
eGFR, mL/min/1.73 m^2, mean (SD)	59 (16.8)	64 (17.5)

[a]Number of patients with serum TTR assessments: CVH, n=191; non-CVH, n=414.

Mortality over the 30-month treatment period, by CVH groups

- Patients with no CVH during the study had a 30-month survival rate of 86.7% (95% CI, 82.9%-89.7%) vs 60.1% (95% CI, 52.8%-66.7%) in patients who had at least one CVH during the study (p<0.0001) (**Figure**)

FIGURE. Kaplan-Meier Curve for Time to ACM Over Month 30 by CVH Groups (mITT Population)



Patients Remaining at Risk (Cumulative Events)

CVH	195 (0)	195 (0)	192 (3)	185 (10)	174 (21)	165 (30)	159 (36)	151 (44)	135 (60)	125 (70)	0 (77)
Non-CVH	416 (0)	413 (3)	407 (9)	404 (12)	399 (17)	392 (24)	389 (27)	382 (34)	375 (41)	367 (49)	0 (54)

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ABBREVIATIONS: ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRwt-CM; wild-type cardiomyopathy; CEC, clinical events committee; CMAD, cardiac mechanical assist device; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; IV, intravenous; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

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