Acoramidis Improves Clinical Outcomes in Patients With Transthyretin Amyloid Cardiomyopathy: Post Hoc Recurrent Event Analyses of ATTRibute-CM

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OBJECTIVE

- **To evaluate the effect of acoramidis vs placebo on the composite endpoints of all-cause mortality (ACM) and recurrent cardiovascular-related hospitalization (CVH)**

INTRODUCTION

- Acoramidis is next-generation transthyretin (TTR) stabilizer being investigated as a treatment for transthyretin amyloid cardiomyopathy (ATTR-CM) with near-complete TTR stabilization (≥90%)[1-4]
- In the phase 3 pivotal study (ATTRibute-CM; NCT03860935), acoramidis demonstrated robust efficacy on clinical outcomes (ACM and first CVH event) based on 2 previously reported analyses: the 2-component, hierarchical Finkelstein-Schoenfeld method (p=0.0182) and the Cox proportional hazards model time-to-first-event analysis (HR=0.645; p=0.0008). However, these analyses did not account for recurrent events[4,5]

METHODS

- Details of the ATTRibute-CM study design have been previously published[4]
- Efficacy analyses were conducted in the modified intent-to-treat (mITT) population (N=611; acoramidis, n=409; placebo, n=202), which included all randomized patients who received ≥1 dose of acoramidis or placebo, had ≥1 efficacy evaluation after baseline and a baseline estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. For randomized patients who received study treatment until Month 30, ACM and recurrent CVH events were collected until Month 30. For randomized patients who discontinued treatment early, ACM was collected at Month 30, whereas recurrent CVH events were censored at 30 days post-treatment discontinuation
- A post hoc analysis was conducted using the Andersen-Gill (A-G) method to evaluate the effect of acoramidis vs placebo on the composite endpoint of ACM or CVH as recurrent clinical events[6,7]
  - The A-G model included treatment group, genotype (ATTR variant-CM vs ATTR wild type-CM), baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (≤3000 vs >3000 pg/mL) and eGFR (≥45 vs <45 mL/min/1.73m^2) as factors, and baseline 6-minute walk test and number of events that occurred before a given interval as covariates
- Negative binomial regression model with treatment group, randomization stratification factors of genotype, NT-proBNP level and eGFR level from Interactive Voice/Web Response System, and the offset term was used to analyze the cumulative CVH or ACM events

CONCLUSIONS

- **Acoramidis demonstrated a highly significant reduction of ACM and recurrent CVH events at Month 30 compared with placebo (by negative binomial regression, relative risk reduction: 42%; p=0.0005)**
- **Results from this post hoc analyses supplement and strengthen the conclusions drawn from the primary analysis of ATTRibute-CM that acoramidis leads to a significant improvement in clinical outcomes (ACM or CVH) in patients with ATTR-CM**

RESULTS

- Of the 632 randomized patients in ATTRibute-CM, 611 were included in the A-G analysis (mITT population)
- Baseline characteristics were comparable across treatment groups (**Table 1**)

TABLE 1. Demographics and Baseline Characteristics (mITT Population)

	Acoramidis n=409	Placebo n=202
Age, years, mean (SD)	77 (6.5)	77 (6.7)
Sex, n (%)		
Male	374 (91.4)	181 (89.6)
Female	35 (8.6)	21 (10.4)
Genetic status, n (%)[a]		
Wild type	370 (90.5)	182 (90.1)
Variant	39 (9.5)	20 (9.9)
NT-proBNP, pg/mL		
Mean (SD)	2865 (2149.6)	2650 (1899.5)
Median (IQR)	2273 (1315-3872)	2274 (1128-3590)
eGFR, mL/min/1.73 m^2		
Mean (SD)	62 (17.4)	63 (17.5)
Median (IQR)	62 (49-74)	61 (48-74)
NYHA class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
Serum TTR, mg/dL		
Mean (SD)	23 (5.6)	24 (6.08)
Median (Q1, Q3)	23 (20.0, 27.0)	23 (20.0, 28.0)

mITT population, N=611. [a]From Interactive Voice/Web Response System stratification factors.
eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

- Over 30 months, ACM and/or recurrent CVH events occurred in 147 (35.9%) and 102 (50.5%) of acoramidis- and placebo-treated patients, respectively (**Table 2**)
- Analysis using the negative binomial regression model demonstrated that treatment with acoramidis led to a reduction in ACM and recurrent CVH events over 30 months compared with placebo (relative risk reduction=42%; p=0.0005) (**Table 2**)
- Analysis using the A-G model (post hoc) showed that treatment with acoramidis led to a significant reduction in ACM and recurrent CVH events over 30 months compared with placebo (risk reduction 30.5%; p=0.0008) (**Table 2**)

TABLE 2. Andersen-Gill and Negative Binomial Regression Model Analyses of ACM and CVH at Month 30 (mITT Population)

	Acoramidis n=409	Placebo n=202
Number of patients with ACM event, n (%)	79 (19.3)	52 (25.7)
Number of patients with CVH[a] events, n (%)	109 (26.7)	86 (42.6)
Total number of ACM or CVH[a] events, n	261	222
Total number of ACM events, n	79	52
Total number of CVH[a] events, n	182	170
Patients with ACM or CVH[a], n (%)	147 (35.9)	102 (50.5)
Total number of ACM or CVH[a] events per patient	0.64	1.10
Negative binomial regression model[b]		
Relative risk ratio vs placebo (95% CI)	0.58 (0.43, 0.79)	
p value	0.0005	
Relative risk reduction[c]	**42%**	
Andersen-Gill model[d]		
HR (vs placebo)	**0.695**	
95% CI[e] of HR	(0.577, 0.838)	
p value	**0.0008**	

mITT population, N=611. [a]Cardiovascular-related hospitalization includes both CEC adjudicated CVH and events of clinical interest. [b]Negative binomial regression model with treatment group, randomization stratification factors of genotype, NT-proBNP level and eGFR level from Interactive Voice/Web Response System, and the offset term was used to analyze the cumulative of CVH or ACM events. [c]Calculated by (1-relative risk ration from the negative binomial regression analysis) x 100%. [d]Stratified by randomization stratification factors (genotype [ATTRv-CM vs ATTRwt-CM], baseline NT-proBNP level [≤3000 vs >3000 pg/mL], eGFR level [≥45 vs <45 mL/min/1.73 m^2]), with treatment group, baseline value of 6MWT and the number of events that occurred before a given interval were included as covariates. [e]Profile likelihood confidence limits are presented.
6MWT, 6-minute walk test; ACM, all-cause mortality; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild type transthyretin amyloid cardiomyopathy; CEC, clinical events committee; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

- The total number of ACM and recurrent CVH events per patient observed was 0.64 (261/409) and 1.10 (222/202) with acoramidis and placebo, respectively, (**Table 2**)
- As previously reported, no safety signals of potential clinical concern were identified in ATTRibute-CM (**Table 3**)[4]

TABLE 3. Safety Summary (Safety Population[a])

Patients with ≥1 event(s)	Acoramidis n=421	Placebo n=211	Overall N=632
Any TEAE, n (%)	413 (98.1)	206 (97.6)	619 (97.9)
TEAEs with fatal outcome	60 (14.3)	36 (17.1)	96 (15.2)
TEAEs leading to hospitalization	212 (50.4)	128 (60.7)	340 (53.8)
TEAEs leading to study drug discontinuation	39 (9.3)	18 (8.5)	57 (9.0)
Any TESAE, n (%)	230 (54.6)	137 (64.9)	367 (58.1)
Any treatment-related TEAE, n (%)	50 (11.9)	11 (5.2)	61 (9.7)

[a]The safety population included all the patients who had undergone randomization and received ≥1 dose of acoramidis or placebo.
TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

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REFERENCES: 1. Penchala SC, et al. *PNAS.* 2013;110(24):9992-9997. 2. Miller M, et al. *Med Chem.* 2018;61(17):7862-7876. 3. Judge DP, et al. *J Am Coll Cardiol.* 2019;74(3):285-295. 4. Gillmore JD, et al. *N Engl J Med.* 2024;390(2):132-142. 5. Judge DP, et al. Presented at AHA (American Heart Association Scientific Sessions) 2023. November 10-13, 2023. Philadelphia, PA. 6. Ozga AK, et al. *BMC Med Res Methodol.* 2018;18(1):2. 7. Thenmozhi M, et al. *Clin Epidemiol Glob Health.* 2019;7(2):253-260.

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