Treatment-Related Early Increase in Serum TTR is Associated With Lower Cardiovascular Mortality in ATTR-CM: Insights From ATTRibute-CM

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OBJECTIVE

- **To prospectively evaluate the impact of treatment-related early increase in serum TTR (also known as prealbumin) on CVM among participants with ATTR-CM from the ATTRibute-CM clinical trial**

CONCLUSIONS

- **This analysis demonstrated that an early and greater increase in serum TTR is significantly associated with lower risk of CVM in ATTR-CM**
- **To our knowledge, this is the first demonstration of the relationship between change from baseline in serum TTR and subsequent risk of CVM in patients with ATTR-CM in a prospective randomized trial**

INTRODUCTION

- ATTR-CM, a progressive disease caused by the destabilization of the TTR tetramer, is associated with poor quality of life and leads to heart failure, hospitalization, and death[1-3]
- Patients with ATTR-CM can have lower circulating serum TTR levels, which are associated with worsening of cardiac function and increased risk of CVM[4]
- Acoramidis is a next-generation, investigational, near-complete (>90%) TTR stabilizer that increases serum TTR levels for the treatment of patients with ATTR-CM[3,5-7]
- ATTRibute-CM (NTC03860935), the phase 3 study of acoramidis vs placebo, met its 4-step primary hierarchical endpoint of mortality, cardiovascular-related hospitalization, change in NT-proBNP, and 6MWT (p<0.0001)[7]
  - Acoramidis was also more effective than placebo in increasing circulating serum TTR levels, and was generally well tolerated

METHODS

- Details of the study design have been previously reported[7]
- Analysis was conducted in the mITT population (N=611; acoramidis, n=409; placebo, n=202), which was the primary analysis population for efficacy endpoints
- CVM was defined as any death due to a cardiovascular or undetermined cause as determined by the Clinical Events Committee up to the 30-month duration. Receiving a heart transplant or a cardiac mechanical assist device was treated as CVM
- The change from baseline in TTR levels was analyzed using the MMRM with J2R method, with treatment group, visit, genotype (ATTRvariant-CM vs ATTRwild type-CM, NT-proBNP levels (≤ 3000 vs >3000 pg/mL), eGFR levels (≥45 vs <45 mL/min/1.73 m^2), treatment group-by-visit interaction as factors, and baseline value as covariate. The genotype, NT-proBNP levels, and eGFR levels randomization stratification factors were based on information from an IXRS
- The relationship between change from baseline in Day 28 serum TTR levels and CVM was analyzed using a stratified Cox proportional hazards model. The model included baseline 6MWT and change from baseline in TTR levels at Day 28 as covariates, and was stratified by treatment group, baseline TTR group (≥20 vs <20), and randomization stratification factors of genotype, NT-proBNP levels, and eGFR levels

RESULTS

- Baseline characteristics were comparable across treatment groups (**Table 1**)[7]

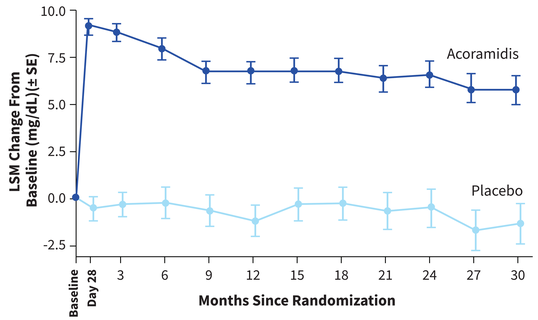
TABLE 1. Demographics and Baseline Characteristics (mITT Population)

	mITT Population N=611	
	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)
NYHA class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
eGFR, mL/min/1.73 m^2		
Mean (SD)	62 (17.4)	63 (17.5)
Median (IQR)	62 (49, 74)	61 (48, 74)
NT-proBNP, pg/mL		
Mean (SD)	2865 (2149.6)	2650 (1899.5)
Median (IQR)	2273 (1315, 3872)	2274 (1128, 3590)
Genetic status, n (%)*		
Wild type	370 (90.5)	182 (90.1)
Variant	39 (9.5)	20 (9.9)

*From IXRS stratification factors.

- The change from baseline in the LSM difference observed between the acoramidis and placebo arms on Day 28 and at Month 30 was 9.6 mg/dL and 7.1 mg/dL, respectively (**Figure**)

FIGURE. Change From Baseline in TTR Levels – MMRM (With J2R) (mITT Population)[7]*



No. at Risk

Acoramidis	406	367	359	353	357	378	376	381	387	398	391	397
Placebo	199	178	177	173	177	188	185	192	195	194	187	197

*Serum TTR levels were analyzed with the use of a MMRM with J2R.

- Approximately 14.9% and 21.3% of participants receiving acoramidis or placebo, respectively, experienced CVM (6.4% absolute risk reduction; 30% relative risk reduction) (**Table 2**)
- The HR from the CVM Cox proportional hazards model for acoramidis vs placebo was 0.709 (95% CI: 0.476, 1.054; nominal p=0.0889), indicating a trend with a 29.1% HR reduction in the risk of CVM compared with placebo

TABLE 2. Summary of CVM (mITT Population)

	Acoramidis (n=409)*	**Placebo (n=202)***
Participants who experienced CVM, n (%)	61 (14.9)	43 (21.3)†
	Cox HR for CVM in the mITT population	
HR	0.709	
p value	0.089	
Cochran-Mantel-Haenszel test	0.037	

*Sample represents all participants in the mITT analysis set.
†1 participant received heart transplantation and 1 participant received a cardiac mechanical assist device.

- Each 1 mg/dL change from baseline TTR increase at Day 28 post-therapeutic intervention was associated with a 5.5% reduction in CVM risk over 30 months. These observations are across the baseline TTR and treatment groups (**Table 3**)

TABLE 3. Cox Proportional Hazards Model of CVM for Each 1 mg/dL Change From Baseline in Serum TTR at Day 28* (mITT Population)

	Acoramidis (n=409)†	**Placebo (n=202)†**
HR	0.945	
95% CI	0.901, 0.922	
p value	0.021	

*Stratified Cox proportional hazards model included baseline 6MWT and change from baseline in TTR levels at Day 28 as covariates, and was stratified by treatment group and randomization stratification factors of genotype, NT-proBNP levels, and eGFR levels as recorded in IXRS and baseline TTR group (≥20 vs <20).
†Sample represents all participants in the mITT analysis set.

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ABBREVIATIONS: 6MWT, 6-minute walk test; ATTR-CM, transthyretin amyloid cardiomyopathy; CVM, cardiovascular mortality; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IQR, interquartile range; IXRS, interactive voice/web response system; J2R, jump to reference; LSM, least squares mean; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

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