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Acoramidis May Improve Cardiac Function and Promote Regression in Transthyretin Amyloid Cardiomyopathy: Data From the ATTRibute-CM Cardiac Magnetic Resonance Substudy

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BACKGROUND

- ATTR-CM is caused by deposition of TTR amyloid fibrils in the myocardium, which can lead to progressive heart failure, significantly impaired quality of life, hospitalization, and premature death.[1,2]
- Acoramidis is a next-generation, oral, investigational, near complete TTR stabilizer with a unique binding mode that mimics the stabilizing properties of the TTR T119M variant.[3,4]
- Acoramidis met its primary hierarchical endpoint of mortality, cardiovascular-related hospitalization, change in NT-proBNP and 6MWD (P<0.0001) in a pivotal Phase 3 study, ATTRibute-CM (NCT03860935).[5]
- CMR with ECV mapping has proven utility in tracking response to treatment in cardiac amyloidosis by assessing changes in cardiac structure, function, and amyloid burden.[6]

OBJECTIVE

- The ATTRibute-CM CMR substudy was conducted to assess changes in cardiac structure, function, and cardiac amyloid burden after treatment with acoramidis or placebo.

METHODS

- Participants enrolled in the phase 3 ATTRibute-CM study from 2 UK sites were included in the CMR substudy.
- CMR was performed as previously described.[6] Inline ECV maps were automatically generated based on hematocrit, as previously described.[6]
- Initial CMR was performed at baseline before the first dose in 35 participants or within 3 months after the first dose in 17 participants (range, 14-105 days); subsequent CMR was performed at months 12, 24, and 30. All CMR images were read centrally at the National Amyloidosis Centre (London) in a fashion blinded to other clinical data.
- ECV values were determined by drawing a region of interest in the basal-mid septum on 4-chamber maps.
  - Amyloid regression was defined as an absolute reduction in ECV of ≥5%, progression was defined as an absolute increase in ECV of ≥5%, and all other ECV changes were considered stable, based on previously published criteria.[7]

RESULTS

Participants

- Fifty-two participants with ATTR-CM from the ATTRibute-CM study enrolled in the CMR substudy (acoramidis: n = 41; placebo: n = 11).
- Twenty-six of 41 participants receiving acoramidis and 5 of 11 receiving placebo completed month 30 scans.
  - Two of 26 and 1 of 5 participants in the acoramidis and placebo groups, respectively, did not undergo ECV mapping at month 30 because of exclusionary renal impairment.
- All-cause mortality was higher in the placebo group (4/11; 36%) than in the acoramidis group (5/41; 12%).

Table 1. Baseline Characteristics and Initial CMR Parameters in the ATTRibute-CM CMR Substudy

	Acoramidis n = 41	Placebo n = 11
Age, median (range), y	76.0 (57.0-86.0)	75.0 (55.0-84.0)
Sex, n (%)		
Male	37 (90.2)	10 (90.9)
Race[a], n (%)		
Black or African American	4 (9.8)	2 (18.2)
White	36 (87.8)	9 (81.8)
ATTRwt-CM, n (%)	35 (85.4)	9 (81.8)
ATTRv-CM, n (%)	6 (14.6)	2 (18.2)
V122I	5 (83.3)	1 (50.0)
T60A	1 (16.7)	1 (50.0)
Years since diagnosis, mean (SD)	1.7 (1.3)	2.3 (1.8)
Initial CMR parameters, mean (SD)		
LVMi, g/m^2	119.4 (21.9)	116.5 (29.5)
LVSVi, mL/m^2	38.6 (11.3)	37.8 (10.3)
LVEF, %	50.7 (12.3)	50.5 (12.0)
LVGLS, %	−10.1 (2.4)	−9.9 (2.5)
RVSVi, mL/m^2	38.4 (10.8)	37.5 (10.3)
RVEF, %	47.6 (12.8)	47.7 (9.0)
ECV, %	61.5 (8.1)	63.8 (7.9)

[a]Multiple races = 1 participant in the acoramidis group

- Baseline characteristics were comparable in both treatment groups (**Table 1**).
- From initial CMR to Month 30, acoramidis demonstrated consistent, favorable trends, relative to placebo, across a range of functional parameters in both ventricles: LV mass index, LV and RV stroke volume index and systolic function (**Figure 1 and Table 2**).

Figure 1. Change From Initial CMR to Month 30

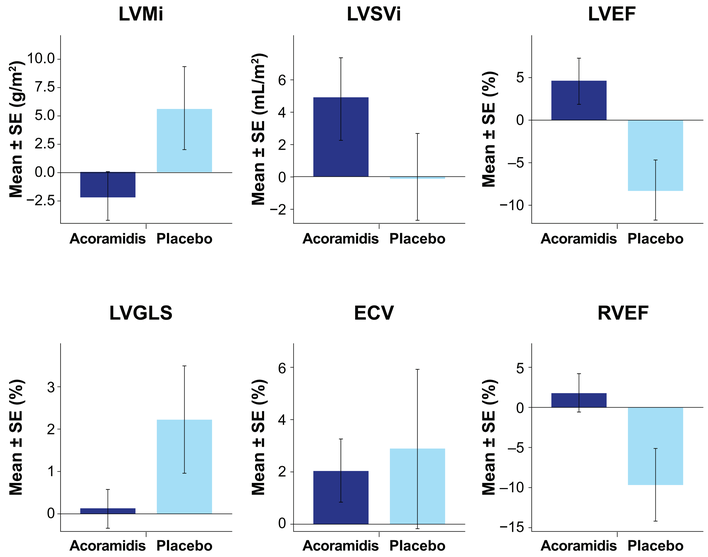
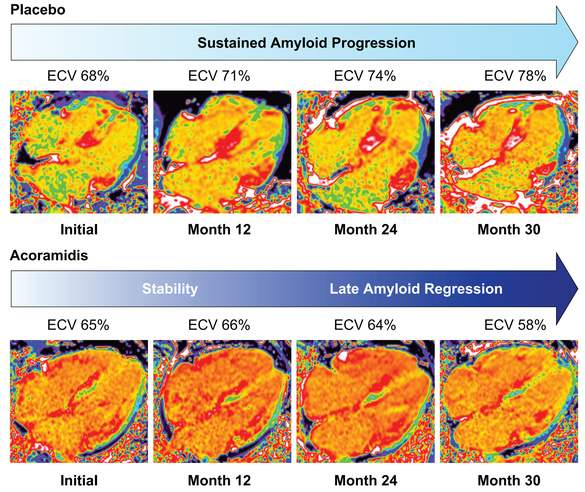


Table 2. Change From Initial CMR to Month 30

CMR parameters, mean change (SD)	Acoramidis	Placebo
LVMi, g/m^2	−2.0 (10.5)	+5.6 (8.3)
LVSVi, mL/m^2	+4.9 (12.2)	+0.0 (5.9)
LVEF, %	+4.6 (13.3)	−8.2 (7.7)
LVGLS, %	+0.1 (2.3)	+2.2 (2.8)
RVSVi, mL/m^2	+4.5 (12.1)	+0.8 (6.8)
RVEF, %	+1.8 (11.7)	−9.6 (9.9)
ECV, %	+2.0 (5.8)	+2.9 (6.0)

Figure 2. Change in ECV From Initial Imaging Over Time



- Amyloid regression was observed in 3/24 (12.5%) of acoramidis recipients; no placebo recipients demonstrated regression (illustrative examples shown in **Figure 2**).

LIMITATIONS

- Findings are reported descriptively as the study was limited by small sample size. Serial CMR could only be conducted in patients who were able to attend follow-up imaging visits, potentially resulting in a survival bias.
- The extent of improvement observed with acoramidis relative to placebo is likely underestimated, as the higher proportion of non-surviving placebo participants may have exhibited accelerated amyloid accumulation with associated deterioration in myocardial function.
- The three participants without ECV mapping may have led to an underestimation in ECV differences.

CONCLUSIONS

- This is the first longitudinal CMR evaluation included within a phase 3 ATTR-CM clinical trial.
- Treatment with acoramidis was associated with cardiac amyloid regression in some participants and a trend toward cardiac structural and functional improvement compared with placebo.
- TTR stabilization with acoramidis may allow the rate of innate amyloid clearance mechanisms to exceed the rate of amyloid formation, thereby enabling cardiac remodelling and functional recovery.
- These findings further inform the mechanism underlying the clinical benefits observed with acoramidis treatment in ATTRibute-CM.

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Abbreviations

ATTR-CM, transthyretin amyloid cardiomyopathy; CMR, cardiac magnetic resonance imaging; ECV, extracellular volume; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; LVMi, left ventricular mass index; LVSVi, left ventricular stroke volume index; MOLLI, modified look-locker inversion; NYHA; New York Heart Association; RVEF, right ventricular ejection fraction; RVSVi, right ventricular stroke volume index; SD, standard deviation; SE, standard error; TTR, transthyretin; v, variant; wt, wild-type.

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Disclosures

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