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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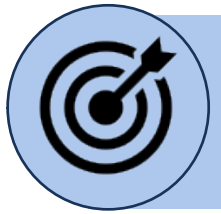
Background

- 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 [1-7]
- Acoramidis is a next-generation, oral, near-complete TTR stabilizer inhibits dissociation of tetrameric TTR into monomers that can form amyloid fibrils [8]
- In ATTRibute-CM*, acoramidis met its primary hierarchical endpoint of mortality, cardiovascular-related hospitalization, change in NT-proBNP and 6MWD (P <0.0001) [10]
- 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. [11]



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.

*ATTRibute-CM (NCT03860935) was a multi-center, double-blind, placebo-controlled, phase 3 ATTR-CM clinical trial to evaluate efficacy and safety of acoramidis. Patients were randomized 2:1 to receive 800mg acoramidis or matching placebo twice daily for 30 months.

6MWD, 6-minute walking distance; ATTR-CM, transthyretin amyloid cardiomyopathy; CMR, cardiac magnetic resonance; ECV, extracellular volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTR, transthyretin.

1. Liz MA, et al. *Neurol Ther* . 2020;9(2):395-402; 2. Vieira M, Saraiva MJ. *Biomol Concepts* . 2014;5(1):45-54; 3. Witteles RM, et al. *JACC Heart Fail* . 2019;7(8):709-716; 4. Rintell D, et al. *Orphanet J Rare Dis* . 2021;16(1):70; 5. Hanna M, et al. *Am J Cardiol* . 2021;141:98-105; 6. Stewart M, et al. *Neurol Ther* . 2018;7(2):349-364; 7. Lauppe R, et al. *ESC Heart Fail* . 2022;9(3):2528-2537; 8. Fox JC, et al. *Clin Pharmacol Drug Dev* . 2020;9(1):115-129; 9. Ji A, et al. Presented at: 2020 International Symposium on Amyloidosis; September 14-18, 2020; 10. Gillmore JD, et al. *N Engl J Med* . 2024;390(2):132-142; 11. Fontana F, et al. *JACC Cardiovasc Imaging.* 2021; 14 (1): 189-199.

Methods

- Participants were invited to enroll in the CMR substudy. All participants provided written informed consent.
- 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) and was performed blinded to other clinical data.
- ECV values were measured by drawing a region of interest in the basal-mid septum on four-chamber maps.
  - Amyloid regression was defined as an absolute reduction in ECV >5%, progression as an absolute increase in ECV >5%, and ECV changes <5% were considered stable.[1]
- Fifty-two participants enrolled in 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.

99mTc, technetium-99m; ATTR, transthyretin amyloid; BID, twice a day; CMR, cardiac magnetic resonance; 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; RVEF, right ventricular ejection fraction, RVSVi, right ventricular stroke volume index

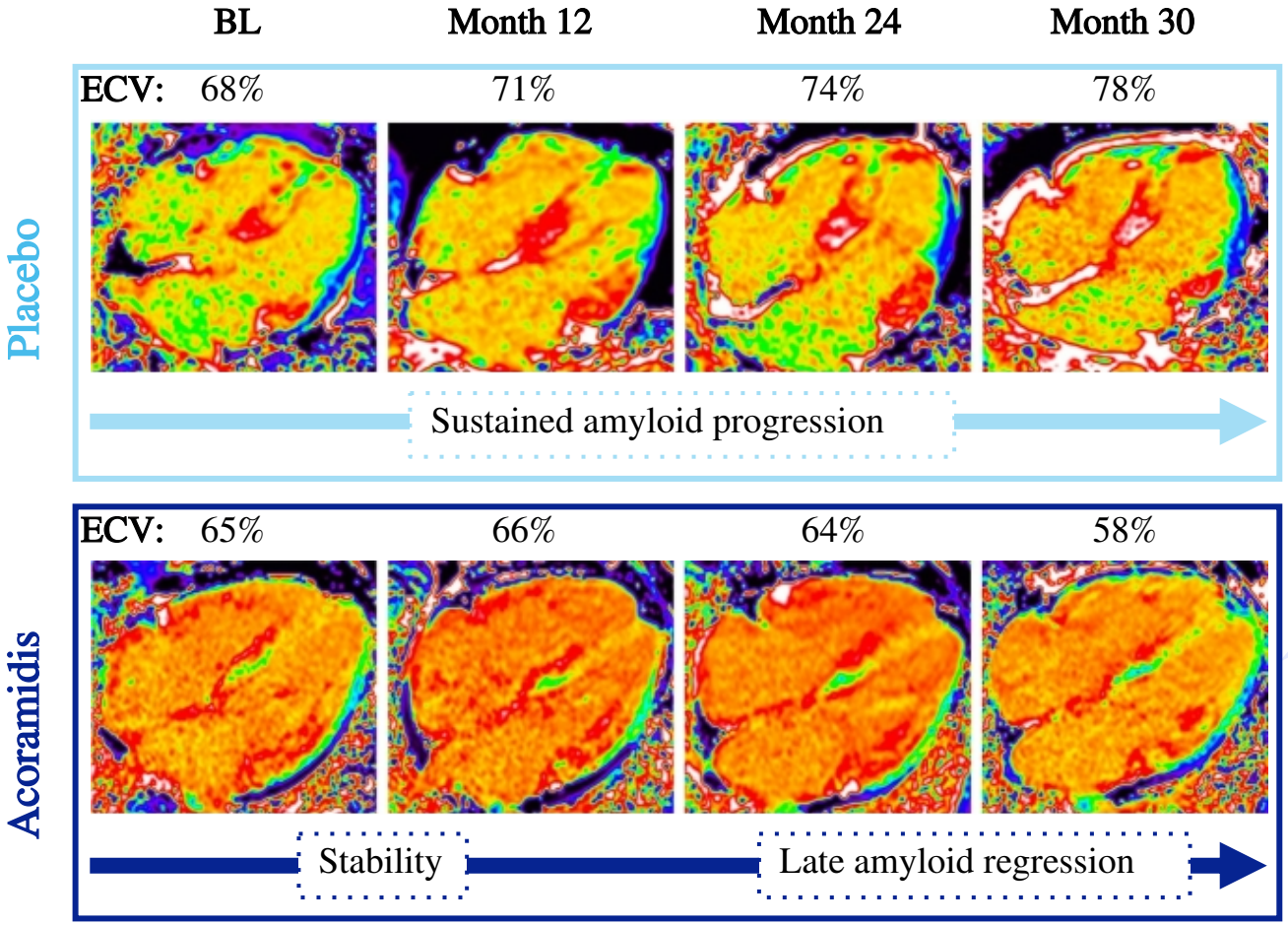
1. Martinez-Naharro A et al. *Eur Heart J.* 2022;43(45):4722-4735

Baseline Characteristics and CMR Parameters were Comparable

Characteristic		Acoramidis (n = 41)	Placebo (n = 11)
Age (years), median (range)		76 (57–86)	75 (55–84)
Male sex, n (%)		37 (90.2)	10 (90.9)
wt-ATTR-CM, n (%)		35 (85.4)	9 (81.8)
vATTR-CM, n (%)	V122I	5 (83.3)	1 (50.0)
	T60A	1 (16.7)	1 (50.0)
Race , n (%)	Black	4 (9.8)	2 (18.2)
	White	36 (87.8)	9 (81.8)
	Multiple races	1 (2.4)	0 (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)

BID, twice daily; CMR, cardiac magnetic resonance; 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; RVEF, right ventricular ejection fraction.

Acoramidis Was Associated With a Trend Toward Reduced ECV From BL to Month 30 Compared With Placebo



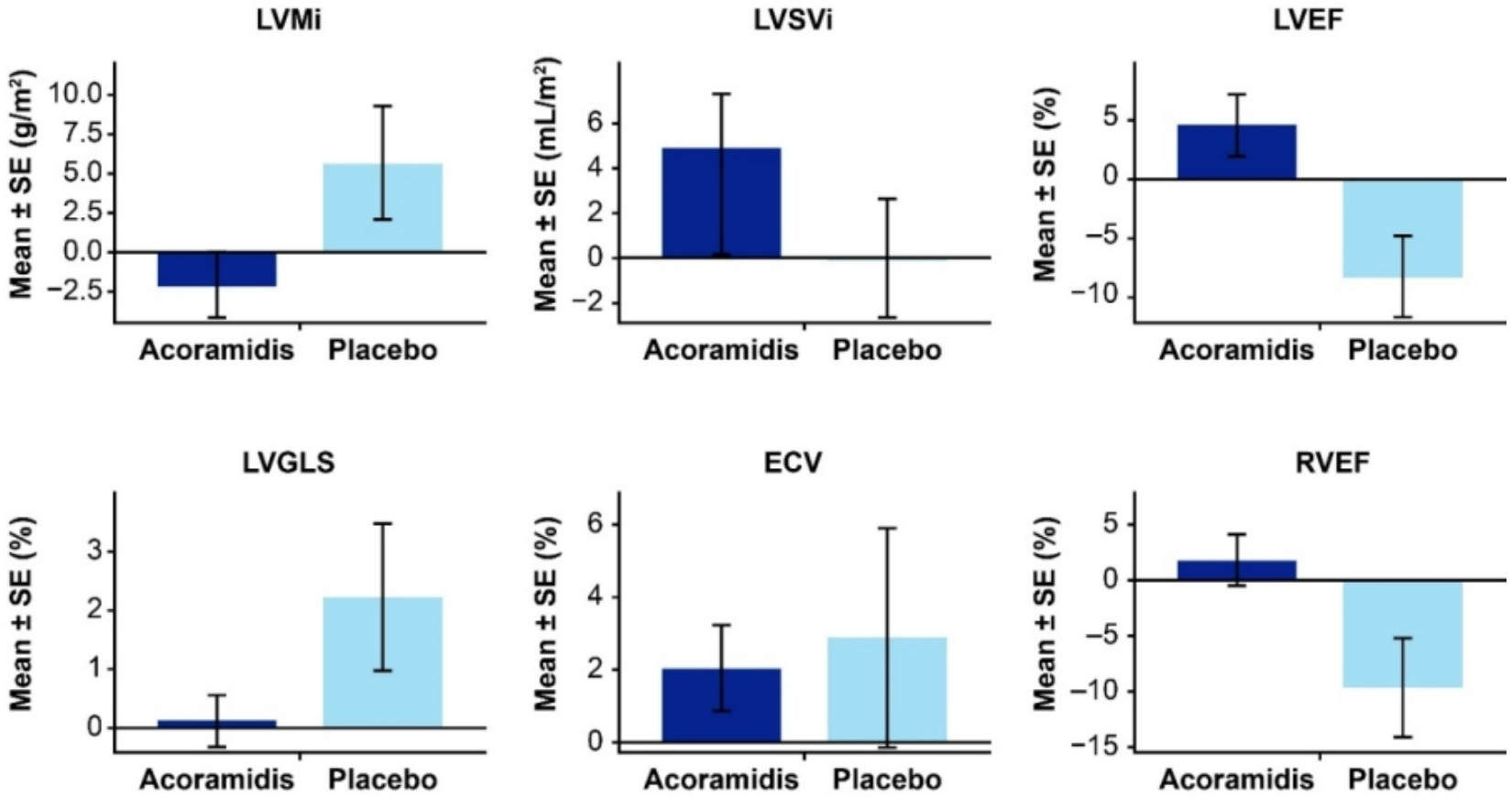
ECV reduction of ≥5% has been shown to indicate cardiac amyloid regression [2] and occurred in 3/26 (12%) patients receiving acoramidis and none receiving placebo at Month 30

Note:

- Three participants (2/26 acoramidis, 1/5 placebo) did not undergo ECV mapping at M30 due to exclusionary renal impairment.

BL, baseline; ECV, extracellular volume

Consistent Improvement in CMR Parameters Was Observed With Acoramidis vs Placebo From Baseline to Month 30



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; RVEF, right ventricular ejection fraction.

Limitations

- Study was limited by small sample size.
- The three participants without ECV mapping may have led to an underestimation in ECV differences.
- Serial data were only available from participants with follow-up imaging visits, potentially adding a survival bias.
  - All-cause mortality was higher in the placebo group (4/11; 36%) than in the acoramidis group (5/41; 12%)
- The extent of improvement observed in acoramidis recipients relative to placebo may have been underestimated
  - Higher proportion of non-surviving placebo participants may have exhibited accelerated amyloid accumulation with associated deterioration in myocardial function had they survived longer.

Conclusion

- 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.