Long-Term Improvement in Myocardial Structure and Function in Patients With Transthyretin Amyloid Cardiomyopathy (ATTR-CM) Treated With Acoramidis Compared With a Natural History Cohort

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PURPOSE

- **To evaluate the proportion of participants with improved cardiac structure and function at Months 30 and 42 of acoramidis treatment in the ATTRibute-CM cardiac magnetic resonance imaging (CMR) substudy**

CONCLUSIONS

- **In the ATTRibute-CM CMR substudy, long-term acoramidis treatment showed improvement in cardiac function and structure in a sizeable proportion of study participants—about a third for LV systolic function and almost a half for LVMi, respectively, in a conservative analysis**
- **These findings suggest an alteration of the expected disease trajectory with acoramidis. A larger study is planned to confirm this effect**

BACKGROUND

- Emerging disease-modifying therapies for ATTR-CM have demonstrated the ability to stabilize disease progression[1,2]
- Increasing evidence suggests that improvement in cardiac structure and function is also achievable in a subset of patients[1–4]
- CMR with ECV mapping is an important tool for assessing changes in cardiac structure, function, and amyloid burden in ATTR-CM and can be used to monitor treatment response[3,4]
  - Analysis of an ATTR-CM natural history cohort at the National Amyloidosis Centre (NAC; London, UK) revealed that untreated patients had a mean increase in ECV of 6.8% over 2 years[1]
  - Increases of 5% in LVEF and 5 mL in LV stroke volume from baseline after 18 months have been associated with subsequent all-cause mortality reductions of 15% and 23%, respectively[2]
- Acoramidis is an oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization and is approved for the treatment of ATTR-CM in the European Union, Switzerland, the UK, the USA, and other countries[5–11]
- In the CMR substudy of the phase 3 ATTRibute-CM study, acoramidis treatment was associated with a trend towards improved or stabilized myocardial CMR parameters including LVEF, LVSVi, and LVMi versus placebo from initial CMR to Month 30[3]
  - The change from baseline in mean (SD) LVEF was +4.6% (13.3%) with acoramidis versus −8.2% (7.7%) with placebo; median (IQR) LVSVi changed by +6.5 (18.0) mL/m² versus −3.0 (7.0) mL/m², respectively, and mean (SD) LVMi changed by −2.0 (10.5) g/m² versus +5.6 (8.3) g/m², respectively
  - ECV was improved in three participants (13%) who received acoramidis[3]
- Long-term effects and efficacy of acoramidis in terms of the percentage of improvers have not been characterized

METHODS

- The study designs of ATTRibute-CM (NCT03860935) and its open-label extension (OLE; NCT04988386) have been previously described[12,13]
  - Participants from two UK sites were included in the CMR substudy[3,14]
- Initial (baseline) CMR was performed 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 ATTRibute-CM Months 12, 24, and 30, and OLE Month 42
- CMR and ECV mapping were performed as previously described.[4] All images were read centrally at the NAC, blinded to other clinical data[3,14]
- The proportions of participants with 'improved' CMR parameters were assessed based on observed data and as per the definitions
- Two analyses were performed

Definitions of 'Improved' for Each CMR Parameter

Parameter	Improved Definition
LVEF	Absolute change from baseline ≥ 5%
LVSVi	Absolute change from baseline ≥ 5 mL/m²
LV systolic function	Improvement in one of two parameters: LVEF or LVSVi; the alternative parameter must be improved or stabilized[a]
LVGLS	Absolute change from baseline ≤ −2%
LVMi	Absolute change from baseline ≤ −5 g/m²
ECV	Absolute change from baseline ≤ −5%

[a]Improved or stabilized LVEF was defined as an absolute change from baseline of > −5%, and improved or stabilized LVSVi was defined as an absolute change from baseline of > −5 mL/m².

Definitions of Completer and Conservative Analyses

Completer Analysis	Conservative Analysis
Included only participants with CMR measurements available at **baseline** and completed CMR assessments at the **designated time point**; participants with missing data at the given time point (Month 24 [NAC natural history cohort], Month 30 [ATTRibute-CM], Month 42 [OLE]) were **excluded**	Included all participants with CMR measurements available at **baseline**; participants with missing data at the given time point (Month 30 [ATTRibute-CM], Month 42 [OLE]) were considered to have neither improved nor stabilized

RESULTS

- Fifty-two participants from ATTRibute-CM were enrolled into the CMR substudy
  - Acoramidis, N = 41; placebo, N = 11
- Overall, participants at baseline had a mean LVEF of 50.6% and LVSVi of 38.4 mL/m². Baseline characteristics and initial CMR parameters were similar in the acoramidis and placebo groups (**Table**)
- A total of 31/52 participants completed CMR scans at Month 30
  - Acoramidis, n = 26; placebo, n = 5
- A total of 33/52 participants continued to receive acoramidis in the OLE
  - Of these, 19 completed CMR scans at Month 42

TABLE: Baseline Characteristics and Baseline CMR Parameters

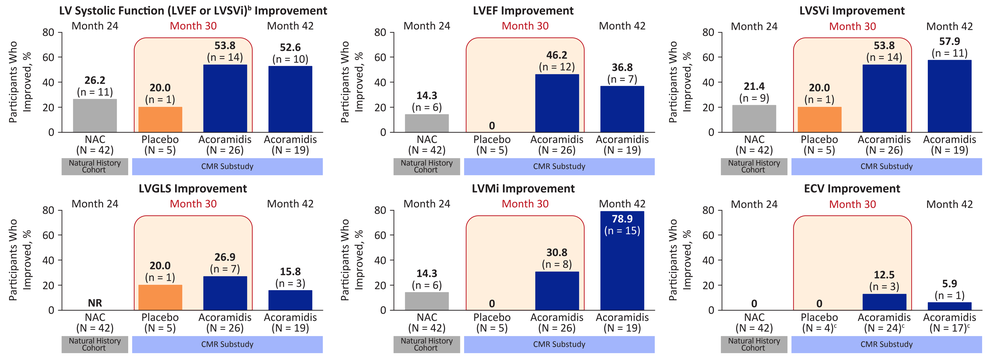
	Placebo (N = 11)	Acoramidis (N = 41)
Age, median (range), years	75.0 (55.0–84.0)	76.0 (57.0–86.0)
Sex, male, n (%)	10 (90.9)	37 (90.2)
Race,[a] n (%)		
Black or African American	2 (18.2)	4 (9.8)
White	9 (81.8)	36 (87.8)
ATTRv-CM, n (%)	2 (18.2)	6 (14.6)
p.Val142Ile	1 (50.0)	5 (83.3)
p.Thr80Ala	1 (50.0)	1 (16.7)
Years since diagnosis, mean (SD)	2.3 (1.8)	1.7 (1.3)
Baseline CMR parameters, mean (SD)		
LVEF, %	50.5 (12.0)	50.7 (12.3)
LVSVi, mL/m²	37.8 (10.3)	38.6 (11.3)
LVGLS, %	−9.9 (2.5)	−10.1 (2.4)
LVMi, g/m²	116.5 (29.5)	119.4 (21.9)
ECV, %	63.8 (7.9)	61.5 (8.1)

[a]One participant in the acoramidis group reported multiple races.

Completer Analysis	Conservative Analysis
• Acoramidis treatment showed favourable trends towards *improvement* from baseline across a range of CMR parameters relative to placebo at Month 30, which continued to Month 42 (**Figure 1**) – For LVGLS at Month 30, although no clinically meaningful difference in the proportion of improvers was observed with acoramidis versus placebo, a higher rate of *improvement or stabilization*[a] versus placebo was observed (76.9% [20/26] vs 40.0% [2/5]) at Month 30, sustained through Month 42 (73.7% [14/19]) • Rates of *improvement* in CMR parameters were low among patients not receiving disease-modifying therapy in the natural history cohort at Month 24	• Acoramidis treatment demonstrated favourable trends towards *improvement* from baseline across a range of CMR parameters assessed at Month 30 compared with placebo, which continued to Month 42 (**Figure 2**) – For LVGLS at Month 30, although no clinically meaningful difference in the proportion of improvers was observed with acoramidis versus placebo, a higher rate of *improvement or stabilization*[a] versus placebo was observed (48.8% [20/41] vs 18.2% [2/11]) at Month 30, sustained through Month 42 (42.4% [14/33])

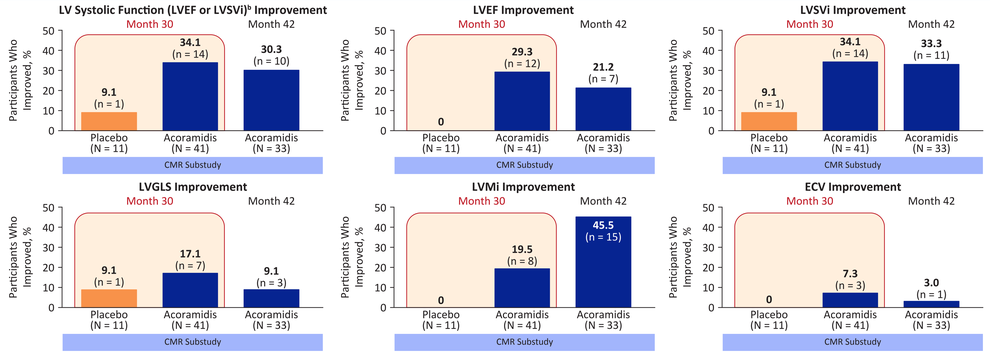
[a]Improvement or stabilization in LVGLS was defined as an absolute change from baseline of < 2%

FIGURE 1: Completer Analysis: Proportions of Participants With Improved CMR Parameters (Observed Data)[a]



[a]The denominator includes participants with CMR available at both baseline and the given time point (Month 24 [NAC], Month 30 [ATTRibute-CM], or Month 42 [ATTRibute-CM OLE]). Participants with missing data at the given time point were excluded from the corresponding completer analysis. [b]The alternative parameter must be improved or stabilized. [c]ECV mapping was not performed for three participants (acoramidis, n = 2; placebo, n = 1) at Month 30 and for two participants (continuous acoramidis) at Month 42.

FIGURE 2: Conservative Analysis: Proportions of Participants With Improved CMR Parameters (Observed Data)[a]



[a]The denominator includes ATTRibute-CM participants with CMR at baseline. Participants with missing data at Month 30 or Month 42 were considered to have neither improved nor stabilized in the corresponding conservative analysis. [b]The alternative parameter must be improved or stabilized.

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ABBREVIATIONS: ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; CMR, cardiac magnetic resonance imaging; ECV, extracellular volume; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; LVMi, indexed left ventricular mass; LVSVi, indexed left ventricular stroke volume; NAC, National Amyloidosis Centre; NR, not reported; OLE, open-label extension; SD, standard deviation; TTR, transthyretin.

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