Anchored Matching-Adjusted Indirect Comparison of Acoramidis (ATTRibute-CM) vs Tafamidis (ATTR-ACT) for Risk of Cardiovascular-Related Hospitalization, All-Cause Mortality, and Safety in ATTR-CM

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PURPOSE

- **To conduct a placebo-anchored, matching-adjusted indirect comparison (MAIC) to compare acoramidis with tafamidis 80 mg for the risk of cardiovascular-related hospitalization (CVH) and all-cause mortality (ACM) in patients with transthyretin amyloid cardiomyopathy (ATTR-CM)**

CONCLUSIONS

- **This placebo-anchored MAIC suggests that treatment with acoramidis led to significantly greater reductions in CVH versus tafamidis 80 mg over 30 months**
- **For ACM, although the point estimate favoured acoramidis, statistical significance was not reached, possibly due to underpower and with treatment duration limited to 30 months**
- **Further head-to-head evaluations or robust real-world evidence are needed to confirm the findings**

BACKGROUND

- ATTR-CM is a progressive cardiomyopathy caused by deposition of destabilized, misfolded transthyretin (TTR) as amyloid fibrils in the heart[1]
- Patients with ATTR-CM develop progressive heart failure, resulting in recurrent CVH, worsening functional status, and often death[1,2]
- Acoramidis and tafamidis are TTR stabilizers approved for the treatment of adults with ATTR-CM in the USA, the European Union, and various other countries[3–10]
- No head-to-head trials exist, and unadjusted indirect comparisons are not appropriate due to differences in enrolment criteria and imbalances between populations that can affect the response to treatment
- Although the ATTRibute-CM and ATTR-ACT study designs were similar, ATTRibute-CM was conducted more recently (**Table 1**)
  - Due to improvements in supportive care and time to diagnosis, participants enrolled in ATTRibute-CM tended to have less-advanced disease than those enrolled in ATTR-ACT, potentially impacting efficacy outcomes relative to the placebo group[11,12]
- An anchored MAIC can reduce bias from cross-trial heterogeneity by reweighting individual participant data (IPD) from the index trial to match aggregate data from the comparator trial, using placebo arms as the common anchor, and resulting in a matched population that balances important differences in baseline characteristics (**Figure 1**)

FIGURE 1: Network Diagram of MAIC of Acoramidis Versus Tafamidis Using the Placebo Group From Both Studies as a Common Comparator

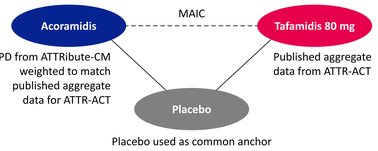


TABLE 1: Overview of the ATTRibute-CM and ATTR-ACT Trials Compared in the MAIC

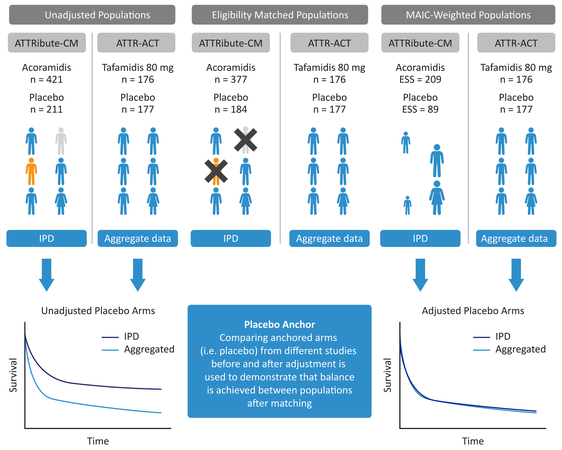
	ATTRibute-CM: Index Trial	ATTR-ACT: Comparator Trial
ClinicalTrial.gov identifier	NCT03860935	NCT01994889
Study design	Phase 3, randomized, double-blind, placebo-controlled	Phase 3, randomized, double-blind, placebo-controlled
Study period	April 2019 through May 2023	December 2013 through February 2018
Randomization	2:1 to acoramidis HCl 800 mg or matching placebo	1:1 to tafamidis 80 mg[a] or matching placebo
Study duration	30 months	30 months
Key eligibility criteria		
Age, years	18–90	18–90
6MWD,[b] m	≥ 150	> 100
NT-proBNP,[b] pg/mL	≥ 300 to < 8500	≥ 600
eGFR,[b] mL/min/1.73 m^2	≥ 15[c]	≥ 25
Primary efficacy endpoint	Composite of ACM, CVH, change from baseline in NT-proBNP level, and change from baseline in 6MWD	Hierarchical assessment of ACM and CVH
ITT population	Acoramidis, n = 421 Placebo, n = 211	Tafamidis 80 mg,[a] n = 176 Placebo, n = 177

[a]Tafamidis 80 mg is the approved dose. The study also included an arm with tafamidis 20 mg, which was matched to placebo 1:2. [b]At screening. [c]Study enrolment criteria cut-off. The primary analysis for efficacy was conducted in participants with eGFR ≥ 30 L/min/1.73 m^2.

METHODS

- In accordance with established methods and guidelines,[13] an anchored MAIC was conducted to estimate the comparative efficacy of acoramidis (ATTRibute-CM; index trial) versus tafamidis 80 mg (ATTR-ACT; comparator trial) (**Figures 1 and 2**)
- Inclusion criteria matching of ATTRibute-CM to ATTR-ACT was done by excluding participants with NT-proBNP level < 600 pg/mL and/or eGFR < 25 mL/min/1.73 m^2
- Potential treatment effect modifiers (EMs) were pre-specified before data analysis based on published evidence and clinical expert input
  - EMs included age, TTR genotype (variant vs wild-type), New York Heart Association (NYHA) functional class, NT-proBNP level, and eGFR
- Comparative efficacy was assessed for ACM and the annualized frequency of CVH over 30 months, using similar definitions for both trials
- Data after initiation of concomitant tafamidis, which was allowed after Month 12 in ATTRibute-CM at the discretion of the investigator, were excluded to avoid potential confounding
- To assess the robustness of the results, sensitivity analyses for CVH and ACM were conducted without censoring for concomitant tafamidis and with matching on baseline medication and pacemaker use
- For safety, no EMs were identified. Naive Bucher indirect treatment comparisons were conducted with and without censoring for concomitant tafamidis

FIGURE 2: Schematic of MAIC-Adjusted Population for Anchored Indirect Comparison



The figure uses colour to indicate inclusion status relative to aligned inclusion/exclusion criteria and icon size to reflect weighting. Blue represents participants aligned with ATTR-ACT inclusion/exclusion criteria and included in the anchored comparison. 'X' denotes ATTRibute-CM participants who were excluded during matching. In the MAIC-weighted populations panel, icon size reflects analytic weight, and the total contribution of the weighted population corresponds to the ESS. The curves in the schematic illustrate the concept of placebo anchoring and do not represent actual data from the trials.

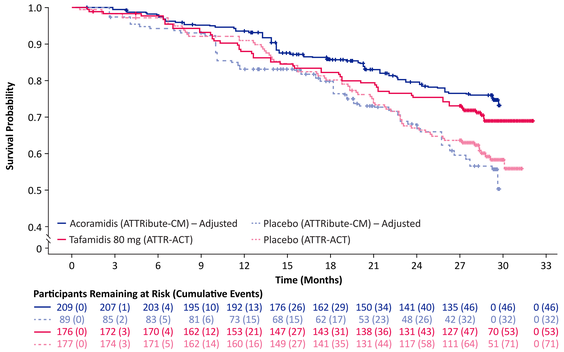
RESULTS

- Matching resolved imbalances in treatment EMs. Post-matching baseline demographics and clinical characteristics in ATTRibute-CM and ATTR-ACT were well balanced (**Table 2**)
- The post-matching effective sample size (ESS) was 209 for acoramidis and 89 for placebo in ATTRibute-CM (**Table 2**)
- Placebo anchor validation: After matching, the Kaplan-Meier curves for ACM in the placebo arms overlapped between trials, demonstrating population alignment for the anchored comparison (**Figure 3**)

TABLE 2: Baseline Demographics and Clinical Characteristics for the ATTRibute-CM Acoramidis and Placebo-Matched Populations and the ATTR-ACT Tafamidis 80 mg and Placebo Arms

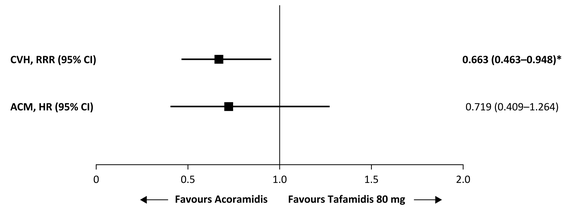
	ATTRibute-CM (Matched)		ATTR-ACT	
	Acoramidis (ESS = 209)	Placebo (ESS = 89)	Tafamidis 80 mg (n = 176)	Placebo (n = 177)
Age, years				
Median (min, max)	76 (50, 88)	75 (55, 89)	76 (46, 88)	74 (51, 89)
< 65, %	9.1	8.5	9.1	8.5
≥ 65, %	90.9	91.5	90.9	91.5
ATTR-CM genotype, %				
Variant	23.9	24.3	23.9	24.3
Wild-type	76.1	75.7	76.1	75.7
NYHA functional class, %				
I	9.1	7.3	9.1	7.3
II	59.7	57.1	59.7	57.1
III	31.2	35.6	31.2	35.6
NT-proBNP, pg/mL				
Mean (SD)	3900 (2100)	3800 (1600)	3900 (3100)	3800 (3000)
Median (min, max)	3100 (400, 15 700)	3200 (500, 8800)	3100 (400, 22 000)	3200 (300, 16 800)

FIGURE 3: Kaplan-Meier Curves for ACM for Acoramidis Versus Tafamidis 80 mg After Matching



- Adjusting for all potential EMs and excluding concomitant tafamidis use, acoramidis was associated with a statistically significant 34% relative risk reduction in the cumulative frequency of CVH versus tafamidis 80 mg (relative risk ratio [RRR]: 0.66; 95% confidence interval [CI]: 0.46–0.95) (**Figure 4**)
- For ACM, after matching, results showed a non-statistically significant 28% hazard reduction versus tafamidis 80 mg (hazard ratio [HR]: 0.72; 95% CI: 0.41–1.26) (**Figures 3 and 4**)
- Across the pre-specified sensitivity analyses, findings were consistent with the base-case MAIC analysis (**Table 3**)
- Safety was comparable between treatments

FIGURE 4: Cumulative Frequency of CVH and ACM for Acoramidis Versus Tafamidis 80 mg After Matching



*Bold indicates statistical significance. Values < 1 indicate a lower risk for acoramidis versus tafamidis 80 mg.

TABLE 3: Sensitivity Analyses for the Cumulative Frequency of CVH and ACM With Additional Matching for Baseline Medication

	Acoramidis ESS	Placebo ESS	Acoramidis vs Tafamidis 80 mg	
			CVH RRR (95% CI)	ACM HR (95% CI)
Base-case MAIC analysis	209	89	0.663 (0.463–0.948)	0.719 (0.409–1.264)
+ RAS	186	83	0.695 (0.480–1.005)	0.762 (0.422–1.377)
+ Diuretics	147	70	0.631 (0.419–0.950)	0.652 (0.351–1.211)
+ RAS + Diuretics	137	66	0.634 (0.417–0.965)	0.690 (0.366–1.302)
+ RAS + Diuretics + Beta blockers + Antithrombotic agents	75	40	0.653 (0.387–1.104)	0.773 (0.366–1.634)
Without censoring for concomitant tafamidis	209	89	0.696 (0.494–0.981)	0.681 (0.395–1.174)

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ABBREVIATIONS: 6MWD, 6-minute walk distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; EM, effect modifier; ESS, effective sample size; HR, hazard ratio; IPD, individual participant data; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAS, renin-angiotensin system-acting agent; RRR, relative risk ratio; SD, standard deviation; TTR, transthyretin.

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