Relative Efficacy of Acoramidis, Tafamidis and Vutrisiran in Patients With Transthyretin Amyloid Cardiomyopathy: A Multilevel Network Meta-Regression

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KEY RESULTS

Results from multilevel network meta-regression (ML-NMR) suggest that acoramidis may reduce cardiovascular-related hospitalization (CVH) over 30 months versus tafamidis 80 mg and vutrisiran in patients with transthyretin amyloid cardiomyopathy (ATTR-CM), with no observed all-cause mortality (ACM) difference at 30 months.

CVH
- Acoramidis versus tafamidis 80 mg: ~24–25% relative risk reduction (numerical difference).
- Acoramidis versus vutrisiran: ~27–33% relative risk reduction (statistically significant with ML-NMR).

ACM
- No significant differences.

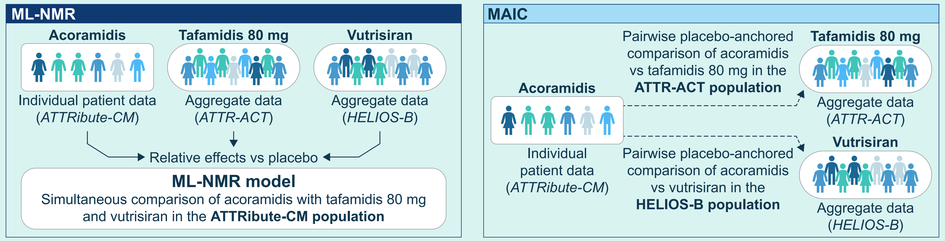
PURPOSE

- To use ML-NMR to indirectly compare acoramidis with tafamidis 80 mg and vutrisiran for reducing CVH and ACM in patients with ATTR-CM.

BACKGROUND

- ATTR-CM is an infiltrative cardiomyopathy resulting from myocardial deposition of amyloid from transthyretin (TTR) protein.[1]
- Available disease-modifying therapies for ATTR-CM act by either stabilizing TTR (acoramidis and tafamidis) or reducing TTR production by RNA interference (vutrisiran).[2–4]
- The efficacy and safety of acoramidis, tafamidis and vutrisiran were evaluated in the ATTRibute-CM (NCT03860935), ATTR-ACT (NCT01994889) and HELIOS-B (NCT04153149) phase 3 trials, respectively.[2–4]
  - Across these trials, all three treatments reduced the risk of CVH and ACM versus placebo in ATTR-CM.[2–4]
- In the absence of head-to-head studies, indirect treatment comparisons (ITCs) are needed.
  - ATTRibute-CM and HELIOS-B were conducted more recently than ATTR-ACT, therefore patients in these trials had less advanced disease owing to improvements in care over time.[1]
- Adjusted ITC approaches, including matching-adjusted indirect comparison (MAIC) and ML-NMR, help to account for differences in baseline treatment effect modifiers between trial populations and minimize bias compared with unadjusted ITCs.
- ML-NMR is an extension of network meta-analysis (with population adjustment) that allows simultaneous comparison of multiple treatments in any target population, whereas MAIC is limited to pairwise comparisons in the comparator trial population (**Figure 1**).

Figure 1. ML-NMR and MAIC adjusted ITC approaches

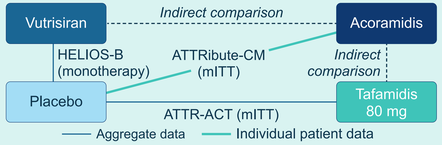


ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression.

METHODS

- An ML-NMR was conducted[5] using individual patient data from the ATTRibute-CM trial and published aggregate data from the ATTR-ACT and HELIOS-B trials (**Figure 2**).[2–4]
- Differences in trial design and baseline demographics and characteristics were assessed before the analysis; key baseline demographics and characteristics are shown in **Table 1**.
- Treatment effect modifiers and prognostic variables were identified based on a literature review and expert input.

Figure 2. Network of evidence included in the ML-NMR



mITT, modified intention-to-treat; ML-NMR, multilevel network meta-regression.

- Effect modifiers adjusted in the final ML-NMR model included age, TTR genotype, New York Heart Association class, N-terminal pro-B-type natriuretic peptide level, estimated glomerular filtration rate, 6-minute walk distance, Kansas City Cardiomyopathy Questionnaire-Overall Summary score, disease duration and diabetes comorbidity at baseline.
- Relative risk ratios for CVH over 30 months and hazard ratios for ACM at 30 months were estimated for acoramidis 800 mg versus tafamidis 80 mg and vutrisiran 25 mg using ML-NMR in the ATTRibute-CM modified intention-to-treat (mITT) population.
  - ATTRibute-CM and HELIOS-B included urgent heart failure visits (also referred to as events of clinical interest) as CVH, whereas ATTR-ACT did not.
  - Urgent heart failure visits were included in the ML-NMR analyses for CVH to optimize the comparison for acoramidis versus vutrisiran.
- ML-NMR results were compared with those estimated using unadjusted Bucher ITCs in the pooled trial populations to help to assess the effect of adjustment on the results.

Table 1. Comparison of key baseline demographics and characteristics between trials

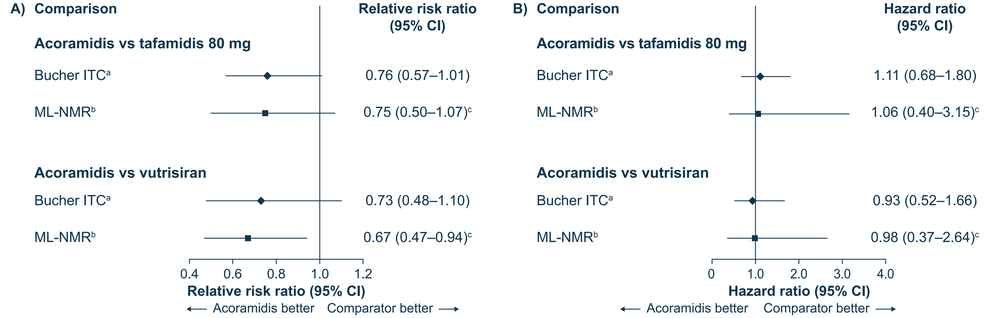
Baseline demographic/ characteristic	ATTRibute-CM (mITT)[2]		ATTR-ACT (mITT)[3,6]		HELIOS-B (monotherapy population)[4]	
	Acoramidis (n = 409)	Placebo (n = 202)	Tafamidis 80 mg (n = 176)	Placebo (n = 177)	Vutrisiran (n = 196)	Placebo (n = 199)
Age, years, median (min, max)	78.0 (50, 90)	77.9 (55, 90)	76.0 (46, 88)	74.0 (51, 89)	77.5 (46, 85)	76.0 (53, 85)
TTR genotype, n (%)						
ATTRv-CM	39 (9.5)	20 (9.9)	42 (23.9)	43 (24.3)	23 (11.7)	25 (12.6)
ATTRwt-CM	370 (90.5)	182 (90.1)	134 (76.1)	134 (75.7)	173 (88.3)	174 (87.4)
Disease duration, years, median (min, max)	0.83 (0, 10.1)	0.71 (0, 7.4)	0.56 (0, 6.9)	0.67 (0, 7.9)	0.50 (0, 8.3)	0.63 (0, 6.2)
NYHA class, n (%)						
I	51 (12.5)	17 (8.4)	16 (9.1)	13 (7.3)	15 (7.7)	12 (6.0)
II	288 (70.4)	156 (77.2)	105 (59.7)	101 (57.1)	172 (87.8)	169 (84.9)
III	70 (17.1)	29 (14.4)	55 (31.3)	63 (35.6)	9 (4.6)	18 (9.0)
NT-proBNP, pg/mL, median (IQR)	2273 (1315, 3872)	2274 (1128, 3590)	3122 (1132, 4019)	3161 (1864, 4825)	2402 (1322, 3868)	1865 (1067, 3099)

ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; IQR, interquartile range; max, maximum; min, minimum; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin.

RESULTS

- Acoramidis was associated with an approximately 24–25% relative risk reduction for CVH versus tafamidis 80 mg over 30 months, although differences were not statistically significant using ML-NMR in the ATTRibute-CM mITT population or Bucher ITC in the pooled trial population (**Figure 3**).
- When compared with vutrisiran, acoramidis was associated with an approximately 27–33% relative risk reduction for CVH.
  - This difference reached statistical significance with ML-NMR in the ATTRibute-CM mITT population but not with Bucher ITC in the pooled trial population (**Figure 3**).
- For ACM, no statistically significant differences were observed between acoramidis and either tafamidis 80 mg or vutrisiran at 30 months using ML-NMR in the ATTRibute-CM mITT population or Bucher ITC in the pooled trial population (**Figure 3**).

Figure 3. (A) Relative risk ratios for CVH over 30 months and (B) hazard ratios for ACM at 30 months with acoramidis versus tafamidis 80 mg and versus vutrisiran



For vutrisiran, adjusted Kaplan–Meier curves from HELIOS-B were used for these analyses.[4]
[a]Without population adjustment, the Bucher ITC target population represents a combination of the ATTRibute-CM and ATTR-ACT or HELIOS-B trial populations, assuming no population differences between trials.
[b]ML-NMR analyses were performed in 559 patients from the ATTRibute-CM mITT population, excluding patients with missing baseline characteristics or with NT-proBNP levels < 600 pg/mL at screening to align inclusion criteria across studies.
[c]95% credible intervals are presented because ML-NMR is implemented in a Bayesian framework.
ACM, all-cause mortality; CI, confidence interval; CVH, cardiovascular-related hospitalization; ITC, indirect treatment comparison; mITT, modified intention-to-treat; ML-NMR, multilevel network meta-regression; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

CONCLUSIONS

- Results of the ML-NMR in the ATTRibute-CM-like population suggest:
  - a numerical reduction in the rate of CVH over 30 months with acoramidis versus tafamidis 80 mg and a statistically significant reduction versus vutrisiran
  - no difference in ACM between acoramidis and tafamidis 80 mg or vutrisiran at 30 months.
- Limitations of this analysis included variability in CVH definitions across trials, a lack of published CVH exposure times in ATTR-ACT and HELIOS-B, and limited assessment of ACM owing to delayed treatment effects and insufficient follow-up.
- Adjusted ITCs are critical to account for differences between trial populations.
- Direct head-to-head treatment comparisons or real-world evidence are required to confirm these findings.

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