Acoramidis Significantly Improves NT-proBNP Indices That Indicate ATTR-CM Disease Progression and Predict Subsequent Mortality: Insights From the ATTRibute-CM Study

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PURPOSE

- **To evaluate the rate of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) progressor indices 1 and 2 observed at various intervals in the ATTRibute-CM efficacy population in patients with symptomatic transthyretin amyloid cardiomyopathy (ATTR-CM)**

BACKGROUND

- ATTR-CM is an infiltrative, restrictive cardiomyopathy caused by the destabilization of transthyretin (aka prealbumin) tetramers[1-5]
- NT-proBNP is a biomarker of disease progression and predicts mortality in ATTR-CM.[6] The following progressor indices have been described:
  - Progressor index 1: an increase in NT-proBNP (>30% and >300 pg/mL) can signal disease progression[6]
  - Progressor index 2: increases in NT-proBNP >500 pg/mL and >1000 pg/mL at Month 12 after diagnosis can predict subsequent mortality in wild-type ATTR-CM[7]
- Acoramidis is a novel, investigational transthyretin oral stabilizer for the treatment of patients with ATTR-CM[8-10]
- The 30-month, phase 3 study of acoramidis vs placebo in ATTR-CM (ATTRibute-CM, NCT03860935; 90% wild-type ATTR-CM) met its four-step primary hierarchical endpoint of mortality, cardiovascular-related hospitalization, change in N-terminal pro-B-type natriuretic peptide, and six-minute walk test (p<0.0001) in the modified intent-to-treat (mITT) population[10]

METHODS

- Details of the study design have been previously published[10]
- The efficacy analysis was conducted in the modified intent-to-treat (mITT) population, which consisted of randomized participants who had a baseline estimated glomerular filtration rate of ≥30 mL/min/1.73 m^2 [10]
- Rates of NT-proBNP progressor indices 1 and 2 (imputed and observed) at 3-month intervals in the ATTRibute-CM study are reported. The denominators for both rates were 409 (acoramidis) and 202 (placebo)
- Cochran-Mantel-Haenszel statistical testing was applied for the comparison of imputed values between groups

CONCLUSIONS

- **Acoramidis treatment leads to significant improvement in NT-proBNP progressor indices as compared to placebo**
- **These results indicate that acoramidis reduces ATTR-CM disease progression, likely resulting in the reduction of subsequent clinical events**

RESULTS

Baseline demographic and disease characteristics

- As previously reported, baseline demographics and clinical characteristics in the intent-to-treat (ITT) population were well balanced between the treatment groups (**Table**)[10]

TABLE. Baseline Demographics and Clinical Characteristics (ITT Population)[10]

	Acoramidis N=421	Placebo N=211
Age, years, mean (SD)	77.4 (6.5)	77.1 (6.8)
Male sex, n (%)	384 (91.2)	186 (88.2)
Transthyretin genotype[a], ATTRv-CM, n (%)	39 (9.3)	19 (9.0)
NT-proBNP, pg/mL, median (IQR)	2326 (1332-4019)	2306 (1128-3754)
eGFR, mL/min/1.73 m^2, mean (SD)	61 (18)	61 (19)
Serum transthyretin, mg/dL, mean (SD)	23 (6)	24 (6)

[a]Genetic status may differ from interactive voice/web response system stratification factor, as classification of a variant for the latter was at the discretion of the investigator. For this electronic case report form, all variants were documented as a mutation.

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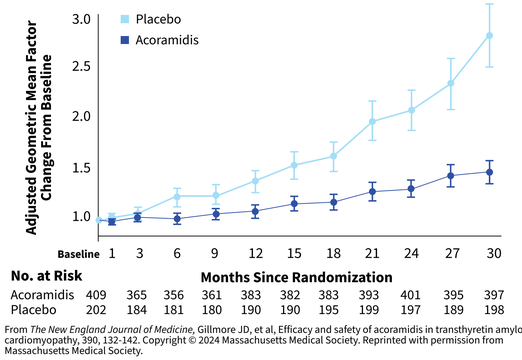
- The rise in NT-proBNP from baseline to Month 30 observed with placebo was attenuated with acoramidis treatment. The ratio of the adjusted geometric mean fold change from baseline to Month 30 between the 2 treatment groups was 0.529 (95% CI: 0.463, 0.604; p<0.0001) (**Figure 1**)

FIGURE 1. Change in NT-proBNP Level From Baseline to Month 30[10]



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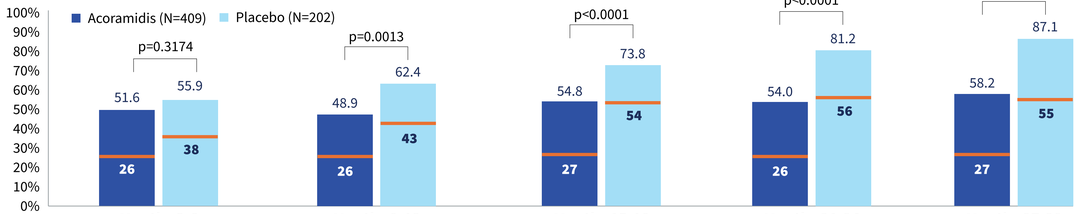
NT-proBNP progressor indices 1 and 2 outcomes

- At all 3-month intervals from end of year 1 (Months 9-12) to the end of the study (Months 27-30), the distribution for both NT-proBNP progressor indices favored acoramidis over placebo (**Figures 2 and 3**)
- For progressor index 1 (imputed values), a 13.5% absolute reduction in the rate of progressors was observed with acoramidis at the end of year 1 (Months 9-12) (p=0.0013) and gradually increased, reaching 28.9% at Months 27-30 (p<0.0001) (**Figure 2**)

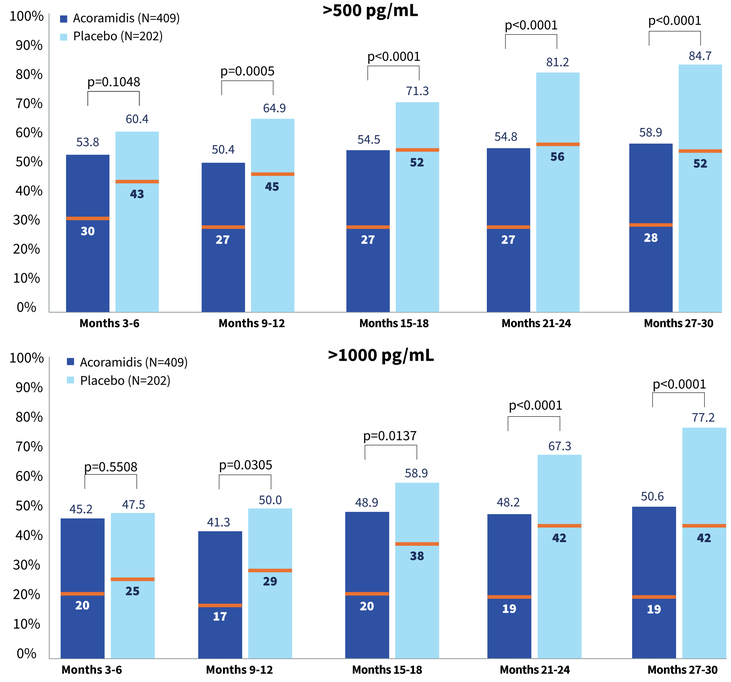
FIGURE 2. Progressor Index 1: Percent of Patients (Imputed and Observed) With NT-proBNP Increase from Baseline (>30% and >300 pg/mL) at Various Intervals[a,b]



[a]The values at the top of the bar are percentage of patients meeting the criteria after imputation (patients with missing data considered as meeting the progression criteria)
[b]The values in the lower base of the bars are percentage of patients meeting the criteria based on observed values

- For progressor index 2 (>500 pg/mL, imputed values), a 14.5% absolute reduction in the rate of progressors was observed with acoramidis at the end of year 1 (Months 9-12) (p =0.0005), gradually increasing to reach 25.8% at Months 27-30 (p<0.0001) (**Figure 3**)
- For progressor index 2 (>1000 pg/mL, imputed values), an 8.7% absolute reduction in the rate of progressors was observed with acoramidis at the end of year 1 (Months 9-12) (p=0.0305), gradually increasing to reach 26.6% at Months 27-30 (p<0.0001) (**Figure 3**)

FIGURE 3. Progressor Index 2: Percent of Patients (Imputed and Observed) With NT-proBNP Increase from Baseline (>500 and >1000 pg/mL) at Various Intervals[a,b]



[a]The values at the top of the bar are imputed values (patients with missing data considered as meeting the progression criteria)
[b]The values in the lower base of the bars are observed values, indicating the percentage of patients who have actually met the criteria at a given visit group

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ABBREVIATIONS: ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant ATTR-CM; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; mITT, modified ITT; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

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REFERENCES: 1. Rapezzi C, et al. *Nat Rev Cardiol*. 2010;7(7):398-408. 2. Ruberg FL, et al. *JAMA*. 2024;331(9):778-791. 3. Lane T, et al. *Circulation*. 2019;140(1):16-26. 4. Ruberg FL, et al. *J Am Coll Cardiol*. 2019;73(22):2872-2891. 5. Grogan M, et al. *J Am Coll Cardiol*. 2016;68(10):1014-1020. 6. Garcia-Pavia P, et al. *Eur J Heart Fail*. 2021a;23(6):895-905. 7. Law S, et al. *Heart*. 2022;108(6):474-478. 8. Penchala SC, et al. *PNAS*. 2013;110(24):9992-9997. 9. Miller M, et al. *Med Chem*. 2018;61(17):7862-7876. 10. Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-142.

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