Acoramidis Treatment Attenuates the Rise in N-Terminal Pro-B-Type Natriuretic Peptide From Baseline to Month 30 Compared With Placebo Across Participant Subgroups in ATTRibute-CM

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PURPOSE

- **To evaluate the effect of acoramidis on N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration across participant subgroups in a post hoc analysis of the ATTRibute-CM study (NCT03860935)**

CONCLUSIONS

- In ATTRibute-CM, acoramidis consistently blunted the 30-month increase in NT-proBNP concentrations by approximately 50% across all participant subgroups assessed, including those with advanced disease, compared with placebo
- These data demonstrate the robust efficacy of acoramidis on NT-proBNP, a key marker of ATTR-CM disease progression
- Furthermore, the efficacy of acoramidis on NT-proBNP concentrations, compared with placebo, was demonstrated independently of concomitant tafamidis use

BACKGROUND

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is an infiltrative, restrictive, life-threatening, and progressive disease caused by destabilized transthyretin (TTR) tetramers and subsequent accumulation of amyloid fibrils in the interstitial space of the myocardium[1–6]
- NT-proBNP is a biomarker of disease progression, and a progressive rise in its concentration is associated with increased mortality[7]
- Acoramidis, an oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in the USA, the European Union, Japan, the UK, and Switzerland for the treatment of adults with ATTR-CM[8–13]
- In the 30-month, phase 3 ATTRibute-CM study,[14] acoramidis treatment significantly attenuated the rise in NT-proBNP concentrations compared with placebo ($p < 0.0001$)
  - Additionally, at Month 30, 45% of acoramidis recipients who had NT-proBNP data available at both baseline and Month 30 experienced a net decrease from baseline in their NT-proBNP concentrations, compared with 9% of those receiving placebo
- The effect of acoramidis on the rise in NT-proBNP concentrations across different patient subgroups has not been fully elucidated

METHODS

- The ATTRibute-CM study design has been described previously[14]
  - Briefly, eligible adult participants (≤ 90 years old) were randomized 2:1 to receive acoramidis HCl 800 mg or placebo twice daily for 30 months
  - Concomitant tafamidis use was permitted after Month 12 at the discretion of the investigator
- Efficacy analyses of NT-proBNP concentrations were assessed in the modified intention-to-treat (mITT) population, which included all randomized participants who received at least one dose of acoramidis or placebo, had at least one efficacy evaluation after baseline, and had a baseline estimated glomerular filtration rate (eGFR) of ≥ 30 mL/min/1.73 m^2
- The adjusted geometric mean (AGM) fold change from baseline to Month 30 in NT-proBNP concentrations was analysed in the acoramidis and placebo treatment groups using a mixed effects model for repeated measures after log transformation of NT-proBNP concentrations
- Missing measurements due to early discontinuation of study drug were imputed using the jump to reference method. Missing measurements due to death were imputed by sampling with replacement from the worst 5% of observed values
- The AGM fold change ratio (acoramidis vs placebo) was calculated for the following pre-specified participant subgroups: ATTR-CM genotype (wild-type vs variant), NT-proBNP (≤ 3000 vs > 3000 pg/mL), eGFR (< 45 vs ≥ 45 mL/min/1.73 m^2), age (< 78 vs ≥ 78 years), country (USA vs rest of world), and New York Heart Association (NYHA) functional class (I/II vs III)
- The change from baseline to Month 30 in NT-proBNP concentrations in participants who completed the study and who received acoramidis alone or placebo alone (i.e. did not receive open-label concomitant tafamidis during the study) was also assessed

RESULTS

- Overall, 611 participants were included in the mITT population; baseline demographics and characteristics were generally well balanced between the treatment groups (**Table 1**)
- Baseline NT-proBNP concentrations for each subgroup are shown in **Table 2**
- In total, 595 randomized participants (acoramidis, n = 397; placebo, n = 198) were included in the Month 30 analysis

TABLE 1: Baseline Demographics and Characteristics; mITT Population (N = 611)

	Acoramidis (n = 409)	Placebo (n = 202)
Age, years, mean (SD)	77.3 (6.5)	77.0 (6.7)
Sex, male, n (%)	374 (91.4)	181 (89.6)
Pre-specified subgroups		
ATTR-CM genotype,[a] n (%)		
ATTRv-CM	39 (9.5)	20 (9.9)
ATTRwt-CM	370 (90.5)	182 (90.1)
NT-proBNP, n (%)		
≤ 3000 pg/mL	268 (65.5)	133 (65.8)
> 3000 pg/mL	141 (34.5)	69 (34.2)
eGFR, n (%)		
< 45 mL/min/1.73 m^2	65 (15.9)	29 (14.4)
≥ 45 mL/min/1.73 m^2	344 (84.1)	173 (85.6)
Age, n (%)		
< 78 years	198 (48.4)	101 (50.0)
≥ 78 years	211 (51.6)	101 (50.0)
Country, n (%)		
USA	77 (18.8)	42 (20.8)
Rest of world	332 (81.2)	160 (79.2)
NYHA functional class, n (%)		
I or II	339 (82.9)	173 (85.6)
III	70 (17.1)	29 (14.4)

[a]TTR genotype was reported at randomization.

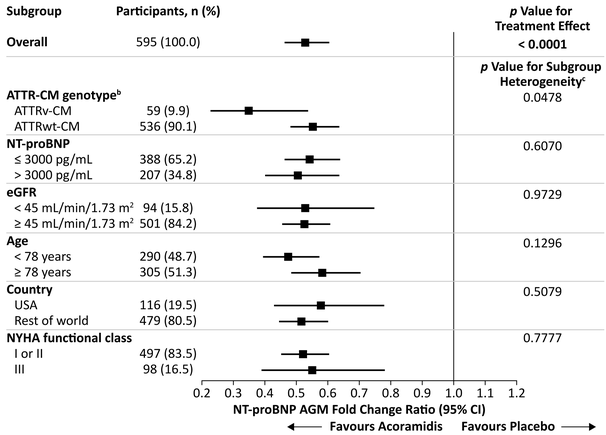
TABLE 2: Baseline NT-proBNP Concentrations in Pre-Specified Participant Subgroups; mITT Population[a] (N = 611)

	NT-proBNP Concentration, pg/mL, Mean (SD)	
	Acoramidis (n = 409)	Placebo (n = 202)
Participants included in the Month 30 analysis, n	397	198
ATTR-CM genotype[b]		
ATTRv-CM	2775.4 (1971.3)	2788.8 (1964.7)
ATTRwt-CM	2874.8 (2169.8)	2634.9 (1897.1)
NT-proBNP		
≤ 3000 pg/mL	1714.2 (955.7)	1597.9 (937.8)
> 3000 pg/mL	5053.3 (2089.8)	4678.3 (1618.1)
eGFR		
< 45 mL/min/1.73 m^2	4063.2 (2350.3)	3693.1 (2273.4)
≥ 45 mL/min/1.73 m^2	2639.0 (2035.4)	2475.3 (1777.9)
Age		
< 78 years	2617.0 (1988.3)	2344.3 (1767.6)
≥ 78 years	3098.4 (2270.8)	2955.9 (1984.7)
Country		
USA	2991.1 (2434.4)	2750.9 (1850.9)
Rest of world	2836.2 (2081.0)	2623.7 (1916.8)
NYHA functional class		
I or II	2724.5 (2104.3)	2520.7 (1845.1)
III	3547.5 (2250.0)	3422.4 (2065.7)

[a]Data shown here are for participants included in the Month 30 analysis (N = 595). [b]TTR genotype was reported at randomization.

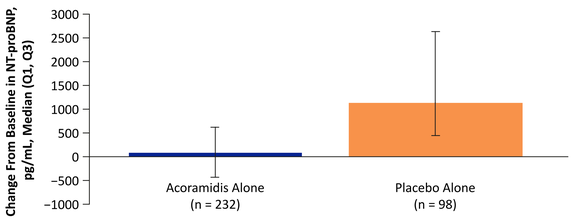
- In all participant subgroups assessed, the NT-proBNP AGM fold change ratio from baseline to Month 30 favoured acoramidis over placebo (all $p < 0.001$), with minimal heterogeneity of treatment effect noted among subgroups (**Figure 1**)
- During the study, 348 participants received acoramidis alone and 156 received placebo alone; data on NT-proBNP concentrations at Month 30 were available for 232 of those receiving acoramidis and for 98 of those receiving placebo
- In participants who completed the study and who received acoramidis alone, the median (Q1, Q3) change from baseline in NT-proBNP concentrations at Month 30 was 86 (−431, 617) pg/mL, compared with 1135 (440, 2634) pg/mL in those who received placebo alone (**Figure 2**)

FIGURE 1: Forest Plot for the NT-proBNP AGM Fold Change Ratio From Baseline Through Month 30 Overall and by Participant Subgroup for Acoramidis Compared With Placebo; mITT Population[a] (N = 611)



[a]Data shown here are for participants included in the Month 30 analysis (N = 595). [b]TTR genotype was reported at randomization. [c]For the treatment effect within each subgroup, all p values were < 0.001.

FIGURE 2: Median Change From Baseline to Month 30 in NT-proBNP Concentrations in Participants Who Received Acoramidis Alone or Placebo Alone (Without Concomitant Tafamidis); mITT Population[a] (N = 611)



[a]Data are shown for participants who did not receive concomitant tafamidis after Month 12 and had data available at baseline and Month 30 (N = 330).

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ABBREVIATIONS: AGM, adjusted geometric mean; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Q1, first quartile; Q3, third quartile; SD, standard deviation; TTR, transthyretin.

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