Robustness of Primary Endpoint Efficacy Results With Acoramidis in ATTR-CM in the ATTRibute-CM Study: Prespecified NT-proBNP Sensitivity Analyses

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OBJECTIVE

- **To evaluate the robustness of the primary hierarchical endpoint of the phase 3 ATTRibute-CM study (NCT03860935) of acoramidis in participants with transthyretin amyloid cardiomyopathy (ATTR-CM) with prespecified sensitivity analyses conducted using various prespecified N-terminal pro-B-type natriuretic peptide (NT-proBNP) thresholds**

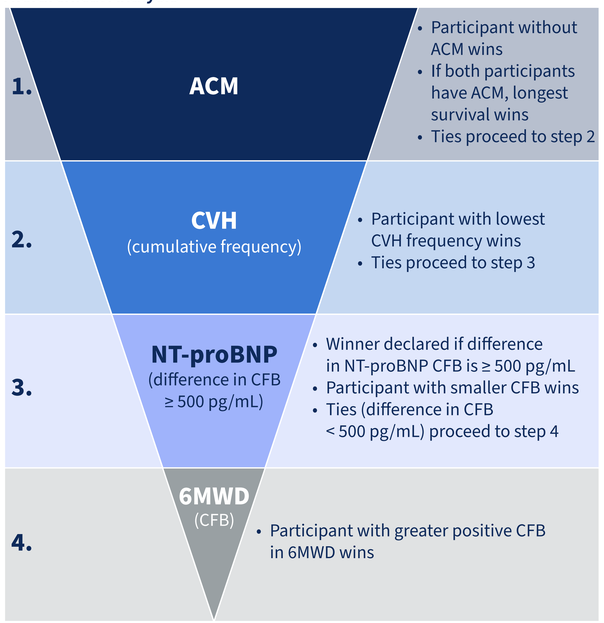
BACKGROUND

- ATTR-CM is a progressive disease characterized by the destabilization of transthyretin (TTR) and aggregation of amyloid fibrils in the heart, leading to progressive heart failure, a significantly impaired quality of life, hospitalization, and death[1–3]
- Acoramidis, a highly selective, oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved by the FDA for the treatment of wild-type or variant ATTR-CM in adults to reduce cardiovascular death and cardiovascular-related hospitalization (CVH). Acoramidis is also approved in Europe for the treatment of wild-type and variant ATTR-CM in adults[4–6]
- In the pivotal phase 3 ATTRibute-CM study in ATTR-CM, acoramidis met its four-step primary efficacy endpoint of all-cause mortality (ACM), frequency of CVH, the difference between participants in change from baseline (CFB) in NT-proBNP levels (threshold ≥ 500 pg/mL), and CFB in 6-minute walk distance (6MWD), compared with placebo ($p < 0.0001$)[7]
- The study design of ATTRibute-CM has been described previously[7]
  - Briefly, participants with ATTR-CM aged 18–90 years were randomized 2:1 to receive acoramidis HCl (800 mg) or matching placebo twice daily for 30 months[7]
  - Efficacy analyses were conducted in the modified intention-to-treat (mITT) population, which consisted of all randomized participants who had 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) ≥ 30 mL/min/1.73 m^2
- In patients with ATTR-CM, a rise in NT-proBNP levels is associated with increased mortality[8]
  - Although a consensus regarding a specific NT-proBNP progression threshold in this population has not been firmly established, recently, an NT-proBNP increase (> 700 pg/mL and > 30%) after 12 months was shown to be associated with subsequent mortality[9]

METHODS

- Two sensitivity analyses pertaining to NT-proBNP were conducted on the primary hierarchical efficacy endpoint
- The primary efficacy analysis was conducted using the Finkelstein-Schoenfeld (F-S) test, which compares pairs of study participants by prioritized sequence (**Figure**)
  - When comparing two participants for CFB in NT-proBNP, a "win" (versus a "tie") was declared when the difference in CFB in NT-proBNP was ≥ 500 pg/mL, the winner being the participant with the lower CFB
- The sensitivity analyses (F-S test) were conducted in the mITT population using more stringent thresholds for the differences between participants in NT-proBNP CFB comparisons, ie, NT-proBNP ≥ 750 pg/mL and ≥ 1000 pg/mL

FIGURE: F-S Scoring Algorithm for the Four-Step Primary Hierarchical Analysis



In pairwise comparisons of NT-proBNP levels at a given visit, a win is declared if the difference in CFB values in NT-proBNP between two study participants is ≥ 500 pg/mL (if so, the participant with the smaller CFB in NT-proBNP wins); if the difference in CFB values between the two participants is < 500 pg/mL, the comparison would be considered a tie. In pairwise comparisons of 6MWD at a given visit, the participant with the greater positive CFB value wins; if the two participants have the same CFB values, the comparison would be considered a tie. The paired comparison for NT-proBNP levels and 6MWD uses the last available nonmissing pair for both participants. A score is assigned with the following rules: win = 1, tie = 0, loss = −1.

CONCLUSIONS

- **Prespecified sensitivity analyses of the four-component hierarchical efficacy endpoint using the more stringent NT-proBNP CFB thresholds of ≥ 750 pg/mL and ≥ 1000 pg/mL consistently demonstrated the efficacy of acoramidis in participants with ATTR-CM**
- **These results point to the robustness of the efficacy of acoramidis compared with placebo observed in the ATTRibute-CM study, even when applying more stringent criteria for what constitutes a clinically meaningful difference in NT-proBNP to indicate disease progression in ATTR-CM**

RESULTS

- In the ATTRibute-CM study, 632 participants were randomized. Of these, 611 participants were included in the mITT population (acoramidis, n = 409; placebo, n = 202)
- Baseline demographics and characteristics of participants in the mITT population were comparable between treatment groups (**Table 1**)

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

Demographic/Characteristic	Acoramidis (n = 409)	Placebo (n = 202)
Age, years, mean (SD)	77.3 (6.47)	77.0 (6.74)
Sex, n (%)		
Male	374 (91.4)	181 (89.6)
Female	35 (8.6)	21 (10.4)
TTR genotype, n (%)[a]		
Wild type	370 (90.5)	182 (90.1)
Variant	39 (9.5)	20 (9.9)
NYHA functional class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
NT-proBNP, pg/mL		
Mean (SD)	2865.3 (2149.64)	2650.1 (1899.48)
Median (IQR)	2273.0 (1315.0–3872.0)	2273.5 (1128.0–3590.0)
eGFR, mL/min/1.73 m^2, mean (SD)	62.0 (17.35)	62.5 (17.53)
Serum TTR, mg/dL, mean (SD)	23.0 (5.58)	23.6 (6.08)

[a]Genetic status as recorded in the interactive voice/web response system at randomization.

- Using more stringent thresholds (≥ 750 and ≥ 1000 pg/mL) for the differences between participants in NT-proBNP CFB comparisons to Month 30 for determining wins, losses, or ties did not impact the statistically significant improvement in the hierarchical endpoint of ATTRibute-CM for acoramidis compared with placebo at Month 30 (all, $p < 0.0001$; **Table 2**)
- As CFB in NT-proBNP levels was tested after ACM and CVH in the F-S test algorithm, the contribution of ACM and CVH to the sensitivity analysis was unaffected

TABLE 2: F-S Analysis for the Hierarchical Combination of ACM, CVH, CFB in NT-proBNP, and CFB in 6MWD at Month 30, With Different NT-proBNP Thresholds; mITT Population (N = 611)

NT-proBNP Threshold Used for Pairwise Comparisons, pg/mL	Test Statistic	*p* Value From F-S Test
500[a]	5.015	< 0.0001
750	4.770	< 0.0001
1000	4.503	< 0.0001

[a]NT-proBNP threshold used in the ATTRibute-CM primary efficacy analysis.

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ABBREVIATIONS: 6MWD, 6-minute walk distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CFB, change from baseline; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; F-S, Finkelstein-Schoenfeld; IQR, interquartile range; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; TTR, transthyretin.

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