Acoramidis-Mediated Improvement in NT-proBNP at Month 30 Compared With Placebo in Patients With ATTR-CM: Results From the ATTRibute-CM Study

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PURPOSE

- **To assess the effect of acoramidis on N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at Month 30 compared with baseline in participants with transthyretin amyloid cardiomyopathy (ATTR-CM) from the phase 3 ATTRibute-CM study (NCT03860935)**

CONCLUSIONS

- Treatment with acoramidis results in a clinically meaningful improvement in NT-proBNP levels and better disease stabilization than placebo. These findings are consistent with the improvements in clinical outcomes observed with acoramidis in ATTRibute-CM
- Further studies are warranted to assess the durability of these effects and implications for the long-term clinical benefits of acoramidis

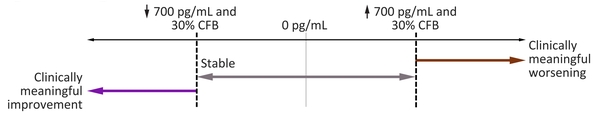
BACKGROUND

- ATTR-CM is a progressive disease characterized by destabilization of transthyretin (TTR), which misfolds, causing the aggregation of amyloid fibrils in the heart.[1–3] This leads to progressive heart failure, impaired quality of life, hospitalizations, and often death[2–4]
- A progressive rise in NT-proBNP levels is a marker of disease progression; studies have shown that an increase of > 300 pg/mL and > 30% in NT-proBNP levels is associated with higher mortality, while others have shown that an increase of > 700 pg/mL and > 30% is associated with an increased risk of death in patients with ATTR-CM[5,6]
- Acoramidis, an oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in the USA, Europe, Japan, and the UK for the treatment of wild-type or variant ATTR-CM in adults[7–11]
- In the phase 3 ATTRibute-CM study, acoramidis reduced the composite of cardiovascular mortality or first cardiovascular-related hospitalization, and blunted the progressive rise in NT-proBNP levels that occurred with placebo[12,13]

METHODS

- The ATTRibute-CM study design has been previously described[12]
- Participants with wild-type or variant ATTR-CM aged 18–90 years were randomized 2:1 to receive acoramidis HCl 800 mg or placebo twice daily for 30 months
  - Efficacy analyses were conducted in the modified intention-to-treat 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 ≥ 30 mL/min/1.73 m^2
- The following analyses were conducted:
  - Proportion of participants with a net (any) decrease in NT-proBNP levels at Month 30, relative to baseline
  - Proportion of participants who had an increase or decrease from baseline at Month 30 in NT-proBNP of (i) > 700 pg/mL and > 30% reduction, and (ii) > 300 pg/mL and > 30% reduction
- NT-proBNP progression categories were further classified as follows (**Figure 1**):
  - Clinically meaningful improvement – decrease of > 700 pg/mL and > 30% from baseline
  - Clinically meaningful worsening – increase of > 700 pg/mL and > 30% from baseline
  - Stable – change in NT-proBNP level at Month 30 not meeting criteria for clinically meaningful disease improvement or worsening
- Results are presented for observed (i.e. including participants with NT-proBNP values available at both baseline and Month 30) and imputed (participants with missing NT-proBNP values at baseline or Month 30, categorized as worsened) analyses

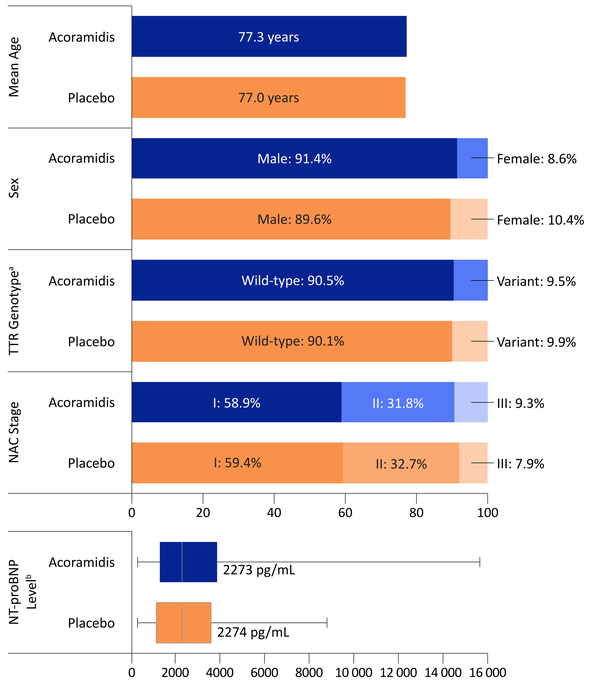
FIGURE 1: NT-proBNP Cut-Off Levels and Percentage Change From Baseline (CFB) for Disease Progression Categories



RESULTS

- Baseline demographics and clinical characteristics were comparable between treatment groups (**Figure 2**)
  - Median (interquartile range) NT-proBNP levels at baseline were similar in the acoramidis and placebo groups (acoramidis: 2273 [1315–3872] pg/mL; placebo: 2274 [1128–3590] pg/mL)[14]

FIGURE 2: Baseline Demographics and Clinical Characteristics by Treatment Group; Modified Intention-to-Treat (mITT) Population (N = 611; Acoramidis, n = 409; Placebo, n = 202)[14]



[a]TTR genotype was reported at randomization. [b]Box plot for NT-proBNP level shows the minimum, quartile 1, median, quartile 3, and maximum values.

- At Month 30, almost half (45%) of the participants receiving acoramidis experienced a net decrease in NT-proBNP levels (any decrease from baseline) compared with 9% of participants receiving placebo (**Figure 3**)

Proportion of Patients With Improved, Stable, or Worsening NT-proBNP Levels, Using a Threshold of 700 pg/mL and 30% Change From Baseline to Month 30

- In the imputed analysis, a greater proportion of acoramidis recipients (54.7%) experienced improved or stable NT-proBNP levels than placebo recipients (25.3%; **Figure 4A**)
- In the observed analysis, improved or stable NT-proBNP levels were observed in 80.0% and 38.3% of participants receiving acoramidis and placebo, respectively (**Figure 4B**)

Using the NT-proBNP progression threshold of 300 pg/mL and 30% change from baseline to Month 30:

- In the imputed analysis, a greater proportion of acoramidis recipients (49.9%) experienced improved or stable NT-proBNP levels than placebo recipients (17.3%)
- In the observed analysis, improved or stable NT-proBNP levels were observed in 72.9% and 26.3% of participants receiving acoramidis and placebo, respectively

FIGURE 3: Proportion of Participants With ATTR-CM in ATTRibute-CM With a Net Decrease in NT-proBNP Levels at Month 30, Compared With Baseline (Observed Dataset; n = 413; Acoramidis, n = 280; Placebo, n = 133)

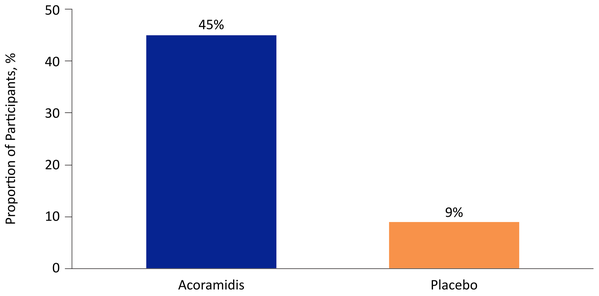
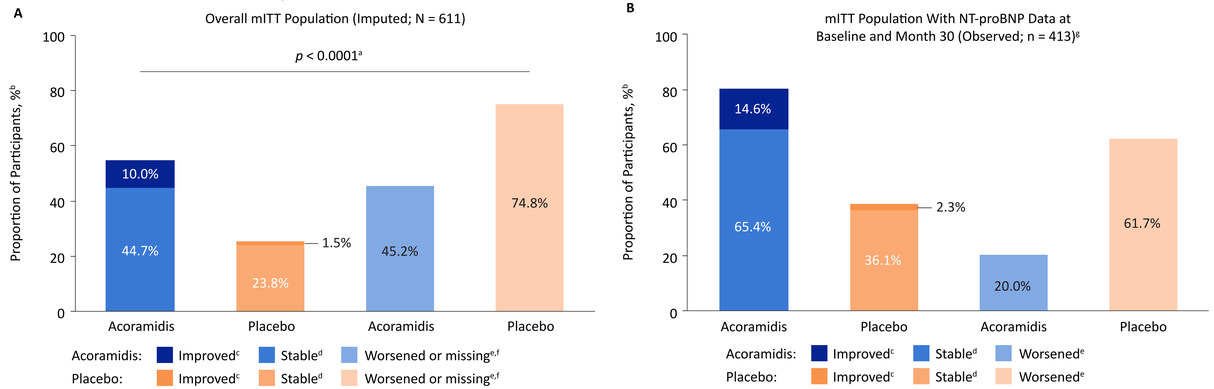


FIGURE 4: Proportion of Participants With ATTR-CM in ATTRibute-CM With Improved, Stable, or Worsened NT-proBNP Levels at Month 30, Relative to Baseline, for A) the Overall mITT Population (Imputed Dataset; N = 611; Acoramidis, n = 409; Placebo, n = 202) and B) Participants With NT-proBNP Data at Baseline and Month 30 in the mITT population (Observed Dataset; n = 413; Acoramidis, n = 280; Placebo, n = 133)



[a]*p* value for acoramidis versus placebo is based on a stratified Cochran-Mantel-Haenszel test with stratification factors of genotype, NT-proBNP level, and estimated glomerular filtration rate as recorded in the interactive voice/web response system at randomization. [b]Values are rounded to one decimal place. Totals may not equal the sum of individual categories due to rounding. [c]Clinically meaningful improvement was defined as a decrease in NT-proBNP level of > 700 pg/mL and > 30% from baseline to Month 30. [d]Stable was defined as a CFB in NT-proBNP level at Month 30 not meeting criteria for clinically meaningful improvement or worsening. [e]Clinically meaningful worsening was defined as an increase in NT-proBNP level of > 700 pg/mL and > 30% from baseline to Month 30. [f]For analysis of the overall mITT population, participants with missing NT-proBNP assessments at baseline or Month 30 were grouped with those who had worsened NT-proBNP levels. [g]Participants who had missing NT-proBNP assessments at baseline and/or Month 30 were not included in this analysis.

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ABBREVIATIONS: ATTR-CM, transthyretin amyloid cardiomyopathy; CFB, change from baseline; mITT, modified intention-to-treat; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTR, transthyretin.

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