Acoramidis leads to clinically meaningful improvements from baseline in NT-proBNP and 6-minute walk distance in patients with transthyretin amyloid cardiomyopathy: observations from ATTRibute-CM

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INTRODUCTION

- Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive myocardial disease leading to repeated cardiovascular (CV) hospitalisations and death within 3–10 years if untreated.[1,2]
- Prognostic factors, such as blood biomarkers and functional assessments, are important indicators of disease course that can guide appropriate management of ATTR-CM.[3]
  - N-terminal pro-B-type natriuretic peptide (NT-proBNP) is an established prognostic marker of CV disease progression;[4] increased NT-proBNP levels (>30% and >700 pg/mL or >30% and >300 pg/mL) are associated with higher mortality[5] or disease progression[6] in people with ATTR-CM.
  - The 6-minute walk distance (6MWD) test is a tool that has been used to denote clinically meaningful progression and improvement (30 m or 35 m change) in functional capacity in other disease states.[7,8]
- Although targeted therapies have shown clinical efficacy, thresholds for clinically meaningful improvements in disease progression and functional capacity in ATTR-CM remain unclear.[9]
  - Advances in imaging and awareness are enabling earlier diagnosis of ATTR-CM, raising questions about whether treatment should still focus solely on slowing progression, or if a subset of patients may achieve clinical improvement.[8]
- Acoramidis, an oral transthyretin (TTR) stabiliser that achieves near-complete (≥90%) TTR stabilisation, is approved in Europe, Japan, the UK and US for the treatment of ATTR-CM.[10–14]
- In the Phase 3 randomised controlled study (ATTRibute-CM; NCT03860935), acoramidis demonstrated significant efficacy in the four-step hierarchical primary endpoint of all-cause mortality, CV-related hospitalisation, and change from baseline in NT-proBNP and 6MWD using the Finkelstein–Schoenfeld method (P<0.0001).[15]
- Results from another analysis reported a net decrease in NT-proBNP levels from baseline to Month 30 in 45% of participants receiving acoramidis compared with 9% receiving placebo.[16]
- Here, we further explore clinically meaningful improvements in NT-proBNP and 6MWD from baseline through 30 months in participants with ATTR-CM from the Phase 3 ATTRibute-CM study.

METHODS

- Details of the ATTRibute-CM study design have been previously published.[12]
- Randomised participants in the modified intent-to-treat (mITT) population (n=611) received acoramidis or placebo (2:1) for 30 months.
- The proportion of participants who met clinically meaningful improvement criteria in NT-proBNP and/or 6MWD was evaluated at Month 30. Participants with missing assessments at Month 30 were categorised as worsened.
  - Participants were stable or improved from baseline if they had no increase of >700 pg/mL and >30% in NT-proBNP levels, or no decrease of >35 m in 6MWD.
  - Clinically meaningful improvements from baseline for NT-proBNP were adopted as the inverse of those used to denote progression (>700 pg/mL reduction and >30% reduction).
  - Clinically meaningful improvement in 6MWD was defined as an increase of >35 m from baseline.
- Univariate logistic regression with the treatment group as an independent variable was performed to compute the odds ratio (OR) and corresponding 95% confidence intervals (CI) for response. The P-value was not multiplicity adjusted, and it must be interpreted as exploratory.

RESULTS

Baseline demographic and disease characteristics

- In the modified intention-to-treat (mITT) population (N=611), 409 participants received acoramidis and 202 received placebo; (**Table 1**).[17]

Table 1. Baseline demographics and clinical characteristics (mITT population)[17]

	Acoramidis n=409	Placebo n=202
Age, mean, years (SD)	77.3 (6.5)	77.0 (6.7)
Male, n (%)	374 (91.4)	181 (89.6)
Transthyretin genotype†, ATTRv-CM, n (%)	39 (9.5)	20 (9.9)
NT-proBNP, pg/mL, median (IQR)	2273 (1315–3872)	2273.5 (1128–3590)
eGFR, mL/min/1.73m², mean (SD)	62.0 (17.4)	62.5 (17.5)
Serum transthyretin‡, mg/dL, mean (SD)	23.0 (5.6)	23.6 (6.1)

†Genetic status may differ from the 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. ‡Serum transthyretin data were available for 406 and 199 participants in the acoramidis and placebo arms, respectively.

ATTRv-CM, hereditary transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; IQR, interquartile range; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

NT-proBNP and 6MWD

- A total of 139 (33.9%) participants in the acoramidis group were stable or improved in either NT-proBNP levels or 6MWD compared with 31 (15.3%) in the placebo group.
- Overall, 93 (22.7%) participants in the acoramidis group showed clinically meaningful improvement in either NT-proBNP levels or 6MWD compared with 18 (8.9%) in the placebo group (OR 3.0, 95% CI 1.8–5.1, P<0.0001; **Table 2** and **Figure 1**).
  - Clinically meaningful improvement was observed in 41 (10.0%) participants for NT-proBNP levels and in 63 (15.4%) participants for 6MWD.
  - Among those meeting both improvement criteria, seven (1.7%) were in the acoramidis group compared with two (1.0%) in the placebo group (OR 1.7, 95% CI 0.4–8.5, P=0.4916).
- Similar results were observed when applying the previously reported NT-proBNP reduction threshold of 300 pg/mL and 30% and the 6MWD threshold of 30 m.

NT-proBNP and 6MWD by genotype

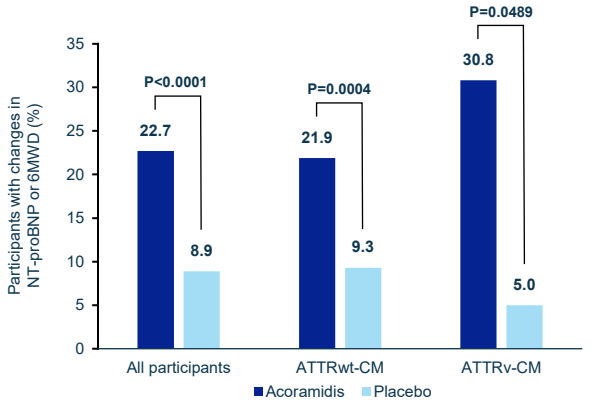
- For participants with wild-type ATTR-CM, 81 (21.9%) acoramidis recipients showed a clinically meaningful improvement from baseline in NT-proBNP levels or 6MWD compared with 17 (9.3%) placebo recipients (OR 2.7, 95% CI 1.6–4.7, P=0.0004; **Table 2, Figure 1**).
- Overall, 12 (30.8%) participants with variant ATTR-CM in the acoramidis group showed clinically meaningful improvement in either NT-proBNP levels or 6MWD compared with one placebo recipient (5.0%; OR 8.4, 95% CI 1.0–70.5, P=0.0489; **Table 2, Figure 1**).

Table 2. Percentage of participants with clinically meaningful improvement in either NT-proBNP (>700 pg/mL reduction and >30% reduction) or in 6MWD (>35 m increase) from baseline at Month 30

All (mITT population)	Acoramidis (n=409)	Placebo (n=202)	Total (N=611)	OR	95% CI	P-value
Clinically meaningful improvement, n (%)	93 (22.7)	18 (8.9)	111 (18.2)	3.0	1.8–5.1	<0.0001
Participants with ATTRwt-CM	**Acoramidis (n=370)**	**Placebo (n=182)**	**Total (N=552)**	**OR**	**95% CI**	**P-value**
Clinically meaningful improvement, n (%)	81 (21.9)	17 (9.3)	98 (17.8)	2.7	1.6–4.7	0.0004
Participants with ATTRv-CM	**Acoramidis (n=39)**	**Placebo (n=20)**	**Total (N=59)**	**OR**	**95% CI**	**P-value**
Clinically meaningful improvement, n (%)	12 (30.8)	1 (5.0)	13 (22.0)	8.4	1.0–70.5	0.0489

Worst-case imputation (participants with missing assessments at Month 30 were categorised as worsened). 6MWD, 6-minute walk distance; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; CI, confidence interval; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio.

Figure 1. Percentage of participants with clinically meaningful improvement in NT-proBNP or improvement in 6MWD from baseline at Month 30



6MWD, 6-minute walk distance; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

CONCLUSIONS

- This post-hoc analysis used a conservative worst-case imputation approach that categorised participants with missing assessments at Month 30 as worsened.
- Even with this conservative approach, ~34% of participants treated with acoramidis and ~15% of participants taking placebo were stable or improved in either NT-proBNP or 6MWD from baseline to Month 30.
- In addition, >22% of participants treated with acoramidis and ~9% of participants taking placebo had clinically meaningful improvements in at least one of the two endpoints (NT-proBNP or 6MWD) from baseline to Month 30 (P<0.0001).
- Consistent improvement with acoramidis was observed across both variant (~31%) and wild-type (~22%) subgroups, reinforcing its broad therapeutic potential.
- These findings support the results from the ATTRibute-CM study and suggest that acoramidis may also lead to clinically meaningful improvements from baseline in markers of ATTR-CM disease severity.

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Conflicts of interest / Disclosures
The presenting author has served as a consultant, advisor or speaker for Alnylam Pharmaceuticals, Amicus Therapeutics, AstraZeneca, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Novo Nordisk and Pfizer.

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