Acoramidis Treatment is Associated With a Lower Incidence of Atrial Fibrillation/Atrial Flutter Events in Patients With ATTR-CM: Insights From the ATTRibute-CM Trial

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*At the time of the study

PURPOSE

- **To evaluate the effects of acoramidis, relative to placebo, on the development of atrial fibrillation (AF) and atrial flutter (AFL) in post-hoc analyses of participants with transthyretin amyloid cardiomyopathy (ATTR-CM) enrolled in ATTRibute-CM (NCT03860935)**

BACKGROUND

- AF is a common manifestation of ATTR-CM, observed in 61–76% of patients, and is associated with an increased risk of cardiovascular-related hospitalization (CVH)[1–3]
- Acoramidis, a highly selective, oral transthyretin (TTR) stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in Europe, the USA, and Japan for the treatment of wild-type and variant ATTR-CM in adults[4–7]
- In the pivotal phase 3 ATTRibute-CM study, acoramidis demonstrated significant clinical efficacy compared with placebo, including a 50% relative risk reduction in the annual frequency of CVH[8,9]
- To date, the effects of acoramidis on events related to AF and AFL in patients with ATTR-CM have not been explored

METHODS

- The ATTRibute-CM study design has been previously described[8]
- Briefly, participants with ATTR-CM aged 18–90 years received acoramidis HCl (800 mg) or matching placebo twice daily for 30 months[8]
- Two post-hoc descriptive analyses were conducted to evaluate the impact of acoramidis on AF/AFL, specifically: 1) the occurrence and annual frequency of CVH due to AF/AFL; and 2) the occurrence of AF/AFL treatment-emergent adverse events (TEAEs)
- CVH due to AF/AFL was determined in a blinded manner by an independent Clinical Events Committee. The annual frequency of these events in each treatment group was analysed in the modified intention-to-treat (mITT) efficacy analysis 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 occurrence of TEAEs related to AF/AFL was evaluated in the overall safety population (all randomized participants who had received at least one dose of acoramidis or placebo) and in the subgroup of participants with no prior AF reported at study entry (no-prior-AF subgroup)
  - AF/AFL TEAEs were identified in the ATTRibute-CM clinical trial database using three Medical Dictionary for Regulatory Activities (MedDRA) preferred terms ('atrial fibrillation', 'atrial flutter', and 'cardiac flutter')

CONCLUSIONS

- **In ATTRibute-CM, acoramidis treatment was associated with lower risks of AF/AFL and CV-related hospitalization due to AF/AFL than placebo**
  - **In the subgroup of participants with no prior AF at study entry, acoramidis treatment reduced the incidence of new-onset AF/AFL compared with placebo**
- **These results suggest potential benefits of acoramidis treatment in reducing new-onset AF/AFL and arrhythmia-associated morbidity, including hospitalization, which is frequently observed in patients with ATTR-CM**

RESULTS

Baseline Demographics and Characteristics

- Baseline demographics and clinical characteristics of the mITT population (N = 611) and the overall safety population (N = 632) were similar (**Table 1**)
- The no-prior-AF subgroup represented 42% of the overall safety population (n/N = 264/632)
- More than 80% of participants in each treatment group of each population had no or mild symptoms of heart failure, categorized as New York Heart Association (NYHA) functional class I or II (**Table 1**)
- Participants in the no-prior-AF subgroup were of comparable age and tended to have lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, higher Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) scores, and a longer 6-minute walk distance (6MWD) than the overall safety population and the mITT population (**Table 1**)

TABLE 1: Baseline Demographics and Characteristics of Participants in the mITT Population, the Overall Safety Population, and the No-Prior-AF Subgroup in ATTRibute-CM

Demographic/Characteristic	mITT Population (N = 611)		Safety Population			
			Overall Safety Population (N = 632)		No-Prior-AF Subgroup (n = 264)	
	Acoramidis (n = 409)	Placebo (n = 202)	Acoramidis (n = 421)	Placebo (n = 211)	Acoramidis (n = 176)	Placebo (n = 88)
Age, years, mean (SD)	77.3 (6.47)	77.0 (6.74)	77.4 (6.45)	77.1 (6.76)	77.1 (6.59)	76.4 (6.44)
Sex, male, n (%)	374 (91.4)	181 (89.6)	384 (91.2)	186 (88.2)	155 (88.1)	75 (85.2)
Wild-type ATTR-CM, n (%)[a]	370 (90.5)	182 (90.1)	380 (90.3)	191 (90.5)	160 (90.9)	75 (85.2)
NYHA class I/II, n (%)	339 (82.9)	173 (85.6)	344 (81.7)	179 (84.8)	148 (84.1)	80 (90.9)
6MWD, m, mean (SD)	362.8 (103.50)	351.5 (93.83)	361.2 (103.70)	348.4 (93.56)	386.8 (105.90)	357.8 (90.12)
NT-proBNP, pg/mL, median (Q1, Q3)	2273.0 (1315.0, 3872.0)	2273.5 (1128.0, 3590.0)	2326.0 (1132.0, 4019.0)	2306.0 (1128.0, 3754.0)	1772.5 (962.5, 2936.0)	1969.0 (861.0, 3222.5)
KCCQ-OS score, mean (SD)	71.7 (19.37)	70.5 (20.65)	71.5 (19.39)	70.3 (20.54)	75.4 (17.27)	73.6 (18.59)

[a]*TTR* genotype was reported in the interactive voice/web response system at randomization.

CV-Related Hospitalization (CVH) Due to an AF/AFL Event

- In the mITT population at Month 30, a smaller proportion of participants who received acoramidis experienced at least one CVH due to an AF/AFL event, compared with those who received placebo (**Table 2**)
- A relative risk reduction in the annual frequency of CVH due to an AF/AFL event of 43% was observed in participants who received acoramidis compared with those who received placebo (**Table 2**)

TABLE 2: CV-Related Hospitalization (CVH) Due to an AF/AFL Event[a]; mITT Population (N = 611)

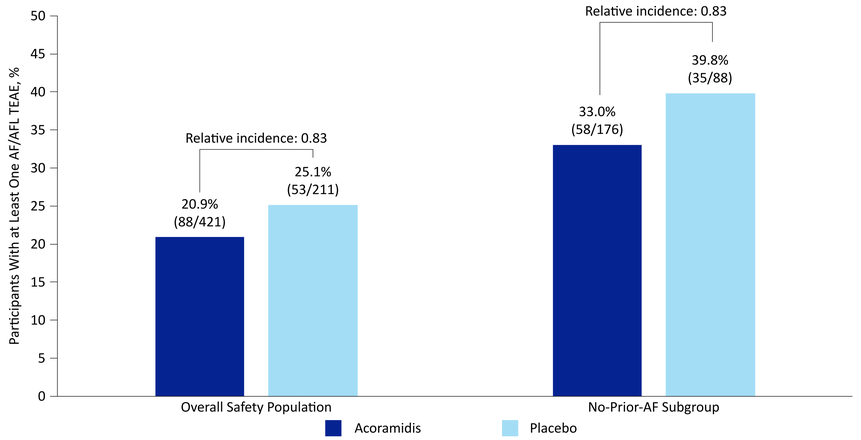
Outcome	Acoramidis (n = 409)	Placebo (n = 202)	Relative Risk Reduction: Acoramidis vs Placebo
Participants with at least one CVH due to an AF/AFL event, n (%)	15 (3.7)	11 (5.4)	–
Annual frequency of CVH due to an AF/AFL event, mean (SD)	0.02 (0.083)	0.03 (0.121)	43%

[a]As determined by an independent Clinical Events Committee.

AF/AFL TEAEs

- In both the overall safety population and the no-prior-AF subgroup, the relative risk of developing an AF/AFL TEAE during the study was reduced by 17% with acoramidis treatment compared with placebo (**Figure**)
  - In the overall safety population, 20.9% of participants in the acoramidis group had at least one AF/AFL TEAE compared with 25.1% of participants in the placebo group
  - In the no-prior-AF subgroup, 33.0% of participants in the acoramidis group had at least one AF/AFL TEAE compared with 39.8% of participants in the placebo group

FIGURE: Occurrence of AF/AFL TEAEs; Overall Safety Population (N = 632) and No-Prior-AF Subgroup (n = 264)



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FUNDING: This study was sponsored by BridgeBio Pharma, Inc., San Francisco, CA, USA.

ABBREVIATIONS: 6MWD, 6-minute walk distance; AF, atrial fibrillation; AFL, atrial flutter; ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; CVH, cardiovascular-related hospitalization; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; MedDRA, Medical Dictionary for Regulatory Activities; 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; TEAE, treatment-emergent adverse event; TTR, transthyretin.

ACKNOWLEDGEMENTS: Under the guidance of the authors, medical writing assistance was provided by Helen Owens, PhD, of Oxford PharmaGenesis and was funded by BridgeBio Pharma, Inc. Editorial support and critical review were provided by Shweta Rane, PhD, CMPP, BCMAS, of BridgeBio Pharma, Inc.

PRESENTED AT: THE ANNUAL CONGRESS OF THE HEART FAILURE ASSOCIATION OF THE EUROPEAN SOCIETY OF CARDIOLOGY (ESC), 17–20 MAY 2025; BELGRADE, SERBIA & ONLINE