Cause of Death in Patients With Transthyretin Amyloid Cardiomyopathy (ATTR-CM): Findings From the ATTRibute-CM Study

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PURPOSE

- **To describe the causes of death in participants with transthyretin amyloid cardiomyopathy (ATTR-CM) enrolled in the ATTRibute-CM study**

BACKGROUND

- ATTR-CM is a progressive disease characterized by destabilization of transthyretin (TTR) and aggregation of amyloid fibrils in the heart, leading to progressive heart failure, significantly impaired quality of life, hospitalizations, and death[1–3]
- Acoramidis, a highly selective, oral TTR stabilizer that achieves near-complete (≥ 90%) TTR stabilization, is approved in Europe, the USA, and Japan for the treatment of wild-type or variant ATTR-CM in adults[4–7]
- In the phase 3 ATTRibute-CM study (NCT03860935) in patients with ATTR-CM,[8] acoramidis treatment was associated with a 42% risk reduction ($p = 0.0005$) in all-cause mortality (ACM) or recurrent cardiovascular-related hospitalization (CVH) versus placebo at Month 30.[9] At Month 42, acoramidis was associated with a 36% risk reduction ($p = 0.0059$) in ACM versus placebo followed by acoramidis, in the 12-month open-label extension[10]

METHODS

- The ATTRibute-CM study design has been described previously[8]
- Participants with ATTR-CM aged 18–90 years were randomized 2:1 to receive oral acoramidis HCl (800 mg) or matching placebo twice daily for 30 months[8]
- Rates of ACM and cardiovascular-related mortality (CVM) over 30 months were assessed in the modified intention-to-treat (mITT) population, which comprised all randomized participants who had received at least one dose of acoramidis or placebo, had at least one post-baseline efficacy evaluation, and had a baseline estimated glomerular filtration rate of ≥ 30 mL/min/1.73 m^2
- The cause of death was adjudicated by an independent Clinical Events Committee
- ACM was defined as death due to any cause, heart transplant, or implantation of a cardiac mechanical assist device (CMAD; commonly known as a ventricular assist device)
- CVM was defined as death due to a cardiovascular (CV) or undetermined cause as adjudicated by the Clinical Events Committee, heart transplant, or CMAD implantation
- The Cochran-Mantel-Haenszel test model was used to compare the rates of ACM and CVM between the acoramidis and placebo groups

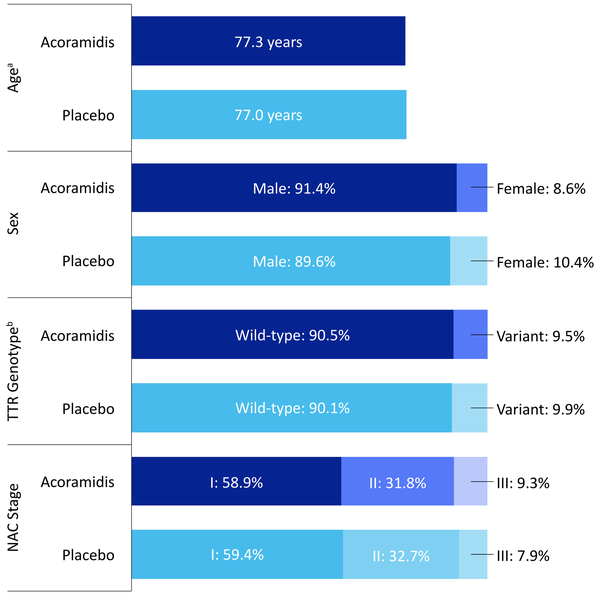
CONCLUSIONS

- **In the ATTRibute-CM study, a 25% relative risk reduction in ACM was observed with acoramidis compared with placebo at Month 30**
- **Most ACM events were CV-related (79%). A 30% relative risk reduction in CVM was observed with acoramidis compared with placebo at Month 30**
- **The most common cause of CV-related death was heart failure**

RESULTS

- Baseline demographics and clinical characteristics were generally balanced between treatment groups (**Figure 1**)[9]

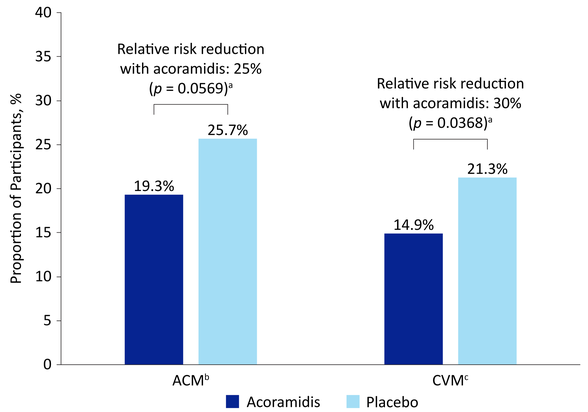
FIGURE 1: Baseline Demographics and Clinical Characteristics by Treatment Group; mITT Population (N = 611; Acoramidis, n = 409; Placebo, n = 202)[9]



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

- Over 30 months, acoramidis treatment demonstrated a numerically lower rate of ACM (acoramidis = 19.3%, placebo = 25.7%; $p = 0.0569$; relative risk reduction = 25%) and CVM (acoramidis = 14.9%, placebo = 21.3%; $p = 0.0368$; relative risk reduction = 30%) compared with placebo (**Figure 2**)

FIGURE 2: Rates of ACM and CVM Over 30 Months; mITT Population (N = 611; Acoramidis, n = 409; Placebo, n = 202)



[a]Calculated from the Cochran-Mantel-Haenszel test of the rate of difference between groups, stratified by randomization stratification factors.
[b]ACM was defined as death due to any cause, heart transplant, or CMAD implantation.
[c]CVM was defined as death due to a CV or undetermined cause as adjudicated by the Clinical Events Committee, heart transplant, or CMAD implantation.

- Causes of ACM and CVM are described in the **Table**
  - The majority of ACM events were CV-related (79.4% [104/131]); of these, heart failure was the most common cause (60.6% [63/104]; 10.3% [63/611] of the overall mITT population) followed by sudden cardiac death (14.4% [15/104]; 2.5% [15/611] of the overall mITT population)
  - For both heart failure and sudden cardiac death, the proportion of participants with events was lower with acoramidis than with placebo
  - Non-CV-related deaths accounted for 20.6% (27/131) of ACM events and were observed at a similar rate in both treatment groups
  - Deaths were assessed as having an undetermined cause in 22 participants

TABLE: Participant Deaths and Adjudicated Causes of Death at Month 30; mITT Population (N = 611)

	Acoramidis (n = 409)	Placebo (n = 202)	Total (N = 611)
ACM, n (%)[a]	**79 (19.3)**	**52 (25.7)**	**131 (21.4)**
Total deaths, n (%)[b]	79 (19.3)	50 (24.8)	129 (21.1)
CV-related, n (%)[c]	61 (14.9)	41 (20.3)	102 (16.7)
Non-CV-related, n (%)	18 (4.4)	9 (4.5)	27 (4.4)
Heart transplant, n (%)	0	1 (0.5)	1 (0.2)
CMAD implantation, n (%)	0	1 (0.5)	1 (0.2)
CVM, n (%)[d]	**61 (14.9)**	**43 (21.3)**	**104 (17.0)**
Deaths due to CV cause, n (%)	48 (11.7)	32 (15.8)	80 (13.1)
Heart failure, n (%)	37 (9.0)	26 (12.9)	63 (10.3)
Sudden cardiac death, n (%)	9 (2.2)	6 (3.0)	15 (2.5)
Stroke, n (%)	1 (0.2)	0	1 (0.2)
Other CV cause (eg, PE, DVT), n (%)	1 (0.2)	0	1 (0.2)
Deaths due to undetermined cause, n (%)	13 (3.2)	9 (4.5)	22 (3.6)
Heart transplant, n (%)	0	1 (0.5)	1 (0.2)
CMAD implantation, n (%)	0	1 (0.5)	1 (0.2)

[a]ACM was defined as death due to any cause, heart transplant, or CMAD implantation.
[b]Cause of death was adjudicated by an independent Clinical Events Committee.
[c]CV-related death was defined as death due to a CV or undetermined cause.
[d]CVM was defined as death due to a CV or undetermined cause as adjudicated by the Clinical Events Committee, heart transplant, or CMAD implantation.

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

ABBREVIATIONS: ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CMAD, cardiac mechanical assist device; CV, cardiovascular; CVH, cardiovascular-related hospitalization; CVM, cardiovascular-related mortality; DVT, deep vein thrombosis; mITT, modified intention-to-treat; NAC, National Amyloidosis Centre; PE, pulmonary embolism; TTR, transthyretin.

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