ATTRibute-CM Study: Scintigraphic Diagnosis and Long-Term Cardiovascular Outcome Benefits of Acoramidis in Transthyretin Amyloid Cardiomyopathy

Kevin M. Alexander,[1] Amrut V. Ambardekar,[2] Francesco Cappelli,[3] Marianna Fontana,[4] Ahmad Masri,[5] Nitasha Sarswat,[6] Keyur Shah,[7] Prem Soman,[8] Chris Chen,[9] Jean-François Tamby,[9] Jonathan C. Fox,[9] Mathew S. Maurer[10]

[1]Stanford University School of Medicine, Palo Alto, CA, USA; [2]University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [3]Careggi University Hospital, Florence, Italy; [4]University College London, London, UK; [5]Oregon Health & Science University, Portland, OR, USA; [6]University of Chicago Medicine, Chicago, IL, USA; [7]Virginia Commonwealth University, Richmond, VA, USA; [8]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [9]BridgeBio Pharma, Inc., San Francisco, CA, USA; [10]Columbia University Irving Medical Center, New York, NY, USA

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OBJECTIVES

- To report diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM) at study entry based on technetium-99m (99mTc) scintigraphy and assess long-term efficacy of continuous acoramidis treatment data from the open-label extension (OLE) of ATTRibute-CM on prespecified secondary outcomes for:

1. Time to cardiovascular mortality (CVM) up to Month 42
2. Time to CVM or first cardiovascular-related hospitalization (CVH) up to Month 42

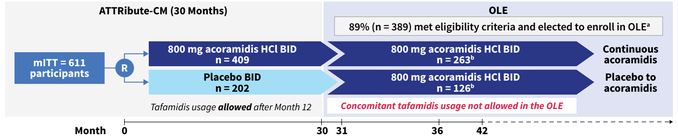
BACKGROUND

- ATTR-CM is a progressive cardiomyopathy resulting in substantial cardiovascular morbidity and mortality caused by destabilization of the transthyretin (TTR) tetramer[1]
- Acoramidis is a highly selective, oral TTR stabilizer that achieves near-complete (≥90%) TTR stabilization and is approved in the USA, Europe, Japan, and UK for treating wild-type or variant ATTR-CM in adults[2-5]
- In the phase 3 ATTRibute-CM study, acoramidis achieved a 36% reduction in all-cause mortality (ACM) or first CVH, and a 42% reduction in ACM or recurrent CVH compared to placebo at Month 30[6,7]
- In the OLE phase of ATTRibute-CM (NCT04988386), continuous acoramidis treatment led to a 36% risk reduction in ACM through Month 42 versus switching from placebo to acoramidis ($p = 0.006$) with no new safety outcomes[8]

METHODS

- Method of diagnosis of ATTR-CM was reported by enrolling sites at study entry
- OLE study design has been published and is shown in **Figure 1**
- CVM and CVH events were adjudicated by an independent clinical events committee
  - CVM included cardiovascular-related death, cardiac mechanical assist device, and heart transplant
  - CVH included cardiovascular hospitalizations (≥24 h) and urgent visits (<24 h) for decompensated heart failure requiring intravenous (IV) diuretics
- Time-to-event analyses (Kaplan-Meier by treatment group) were done using a stratified Cox proportional hazards model with treatment group as an explanatory factor and baseline 6-minute walk distance as a covariate, stratified by genotype, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, and estimated glomerular filtration rate, as recorded in the interactive voice/web response system

FIGURE 1. ATTRibute-CM OLE Study Design



Key OLE Eligibility Criteria

- Completed 30 months of study treatment in ATTRibute-CM
- Discontinued concomitant tafamidis use before entering OLE
- No planned concomitant tafamidis or other investigational treatment during OLE

OLE Endpoints[c]

Time to first event for CVM and CVM or first CVH[d,e]

Figure adapted from: Judge DP, et al. *Circulation* 2025;151(9):601–611. (https://creativecommons.org/licenses/by/4.0/).
[a]11% elected not to enroll into the OLE (n = 49), most commonly due to desire to receive tafamidis after ATTRibute-CM. [b]mITT analysis was continuous from the start of ATTRibute-CM into the OLE. [c]For this study. [d]Cox proportional hazards model. [e]CVH was defined as a non-elective admission to an acute care setting for CVM that resulted in at least a 24-hour stay, or an unplanned visit to an emergency department/ward, urgent care clinic, or day clinic of fewer than 24 hours for the management of decompensated heart failure requiring treatment with an intravenous diuretic.

CONCLUSIONS

- In ATTRibute-CM, 99mTc scintigraphy contributed to diagnosis in more than 75% of patients with ATTR-CM enrolled
- Acoramidis treatment administered for 42 months led to a 42% relative risk reduction in CVM compared with placebo to acoramidis treatment
- Acoramidis treatment administered for 42 months led to a 38% relative risk reduction in time to CVM or first CVH compared with placebo to acoramidis treatment, with a benefit observed as early as 3 months after treatment initiation
- Findings demonstrate the long-term clinical benefits of acoramidis, a near-complete TTR stabilizer, for reducing CVM in ATTR-CM, as well as the importance of early treatment

RESULTS

Participants and Participant Characteristics

- Diagnosis of ATTR-CM in ATTRibute-CM was based on non-invasive means only (ie, 99mTc scintigraphy and serum testing for ruling out light-chain amyloidosis) in 75.9% (464/611) of study participants and by endomyocardial biopsy in 24.1% (147/611) of study participants
- Overall, 389 participants enrolled in the OLE and received open-label acoramidis, of whom 263 received continuous acoramidis and 126 switched from placebo to acoramidis
- Participant characteristics of the treatment groups at entry into the OLE were mostly similar (**Table 1**)
  - Participants in the placebo-to-acoramidis group had higher median NT-proBNP levels (2905 vs 2094 pg/mL) and a higher proportion of New York Heart Association (NYHA) Class III (35.7% vs 16.7%)

TABLE 1. Participant Characteristics at Entry Into the OLE

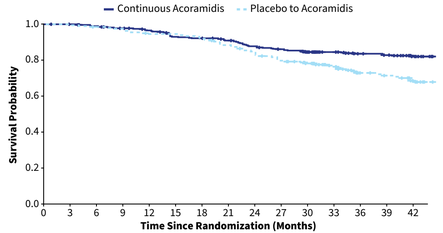
Participant Characteristics[a,b]	Continuous Acoramidis (n = 263)	Placebo to Acoramidis (n = 126)
Age, years, mean (SD)[c]	78.8 (6.50)	79.7 (6.33)
Male sex, n (%)	244 (92.8)	115 (91.3)
Wild-type ATTR-CM, n (%)[d]	242 (92.0)	120 (95.2)
ATTR-CM duration at randomization,[d,e] years		
n	262	126
Mean (SD)	1.2 (1.10)	1.2 (1.29)
NYHA class, n (%)[f]		
I or II	216 (82.1)	79 (62.7)
III	44 (16.7)	45 (35.7)
IV	3 (1.1)	1 (0.8)
NT-proBNP, pg/mL		
n	257	125
Median (IQR)	2094.0 (1247.0–3566.0)	2905.0 (1624.0–5166.0)
Serum TTR, mg/dL		
n	258	124
Mean (SD)	32.8 (6.22)	25.6 (6.53)
Participants who received tafamidis in the ATTRibute-CM study, n (%)	29 (11.0)	23 (18.3)

Table adapted from: Judge DP, et al. *Circulation* 2025;151(9):601–611. (https://creativecommons.org/licenses/by/4.0/).
[a]Data are for all participants who enrolled in the OLE and received at least one dose of open-label acoramidis. [b]Baseline values are the last non-missing assessment values completed before the first OLE acoramidis treatment. [c]Age calculated from the first OLE treatment date and date of birth/age from 'Date of Birth' in the electronic case report form. [d]Data at the time of randomization in ATTRibute-CM (not at OLE entry). [e]Calculated as (randomization date – date of ATTR-CM diagnosis)/365.25. [f]Data missing for one participant in the placebo-to-acoramidis group.

Time-to-Event Analysis of CVM

- At Month 42, CVM events (n = 126) constituted the majority (76.8%) of ACM events (n = 164)
- CVM through Month 42 occurred in 16.6% of patients in the continuous acoramidis group versus 28.7% in the placebo-to-acoramidis group (**Figure 2**)
  - This corresponds to a 42.1% relative risk reduction for CVM in the continuous acoramidis group versus the placebo-to-acoramidis group

FIGURE 2. Continuous Acoramidis Reduced the Risk of CVM Through Month 42 Versus Placebo to Acoramidis (mITT Population)



Participants Remaining at Risk (Cumulative Events)

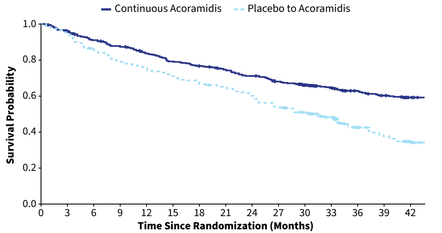
Continuous Acoramidis	409 (0)	407 (0)	401 (4)	393 (9)	385 (14)	369 (28)	365 (31)	358 (36)	344 (49)	366 (55)	297 (61)	260 (61)	247 (64)	243 (66)	216 (68)
Placebo to Acoramidis	202 (0)	201 (1)	198 (3)	196 (5)	188 (11)	188 (11)	183 (16)	175 (23)	166 (31)	156 (40)	143 (43)	118 (46)	102 (51)	98 (53)	87 (58)

	Continuous Acoramidis (n = 409)	Placebo to Acoramidis (n = 202)
CVM, n (%)	68 (16.6)	58 (28.7)
Relative risk reduction	**42.1%**	
Hazard ratio (95% CI)	0.56 (0.389–0.791)	
***p* value**	0.0011	

Time-to-Event Analysis of CVM or First CVH

- The composite endpoint of CVM or first CVH through Month 42 occurred in 38.4% of patients in the continuous acoramidis group versus 61.4% in the placebo-to-acoramidis group (**Figure 3**)
  - Continuous acoramidis treatment demonstrated a 37.5% relative risk reduction compared with placebo to acoramidis

FIGURE 3. Continuous Acoramidis Reduced the Risk of CVM or First CVH Through Month 42 Versus Placebo to Acoramidis (mITT Population)



Participants Remaining at Risk (Cumulative Events)

Continuous Acoramidis	409 (0)	389 (18)	370 (36)	355 (50)	337 (66)	319 (84)	308 (94)	298 (102)	284 (116)	270 (128)	233 (136)	203 (140)	189 (146)	179 (154)	156 (157)
Placebo to Acoramidis	202 (0)	191 (11)	172 (29)	159 (42)	152 (49)	143 (58)	135 (66)	129 (71)	121 (79)	108 (92)	97 (99)	80 (103)	63 (112)	54 (119)	45 (124)

	Continuous Acoramidis (n = 409)	Placebo to Acoramidis (n = 202)
CVM, n (%)	157 (38.4)	124 (61.4)
Relative risk reduction	**37.5%**	
Hazard ratio (95% CI)	0.54 (0.429–0.691)	
***p* value**	< 0.0001	

CORRESPONDING AUTHOR: Kevin M. Alexander, kevalex@stanford.edu.

PRESENTING AUTHOR: Kevin M. Alexander.

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ABBREVIATIONS: 99mTc: technetium-99m; **ACM:** all-cause mortality; **ATTR-CM:** transthyretin amyloid cardiomyopathy; **BID:** twice daily; **CI:** confidence interval; **CVH:** cardiovascular-related hospitalization; **CVM:** cardiovascular mortality; **IQR:** interquartile range; **IV:** intravenous; **mITT:** modified intent-to-treat; **NT-proBNP:** N-terminal pro-B-type natriuretic peptide; **NYHA:** New York Heart Association; **OLE:** open-label extension; **R:** randomization; **SD:** standard deviation; **TTR:** transthyretin.

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