ATTRibute-CM: ITT Sensitivity Analysis and Sub-Analysis Comparing Acoramidis and Placebo in Stage 4 CKD

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Presenter: Steen Poulsen

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Background

- ATTR-CM, caused by destabilization of TTR, can lead to progressive heart failure, significantly impaired quality of life, hospitalization, and premature death[1,2]
- **Acoramidis** is a next-generation, investigational TTR stabilizer that demonstrated **robust clinical efficacy vs placebo in a pivotal phase 3 study, ATTRibute-CM***[3-5]
- Acoramidis treatment is associated with a **25% relative risk reduction in all-cause mortality** in a prespecified mITT population with **eGFR ≥30 mL/min/1.73 m²**[5]
- **Patients with eGFR <30 mL/min/1.73 m² (Stage 4 CKD)** were enrolled in the trial to explore safety in this high-risk subpopulation, but were excluded from the primary mITT efficacy analysis; the ITT population was defined as the mITT population + participants with stage 4 CKD

OBJECTIVE:

We report the results of a prespecified ITT sensitivity analysis that includes a high-risk subgroup with stage 4 CKD from ATTRibute-CM

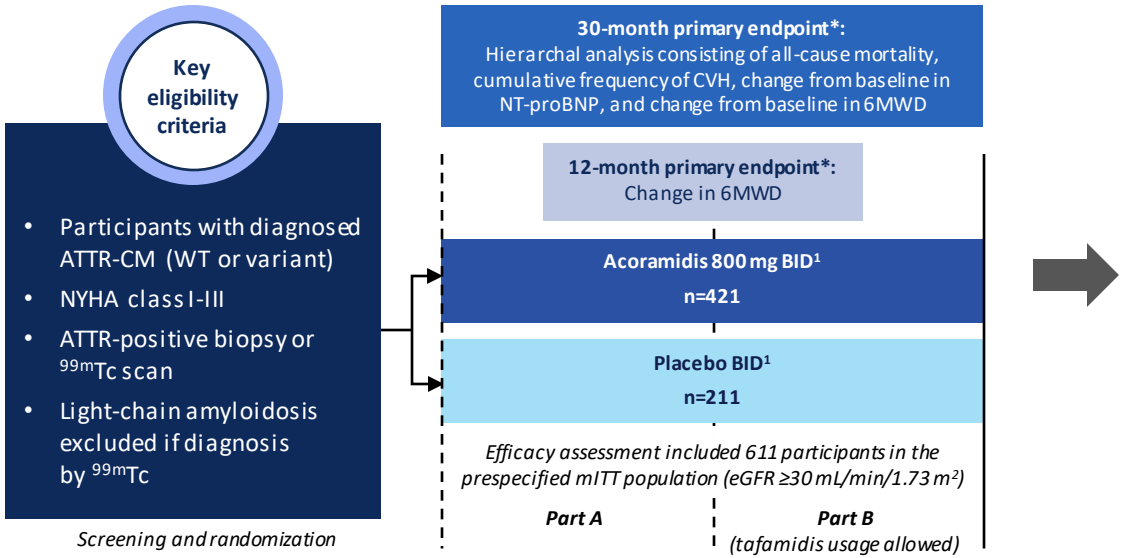
*ATTRibute-CM (NCT03860935) was a multicenter, double-blind, placebo-controlled, phase 3 ATTR-CM clinical trial. Patients were randomized 2:1 to receive 800 mg acoramidis or matching placebo twice daily for 30 months. It met its primary hierarchical endpoint of mortality, cardiovascular-related hospitalization, change in NT-proBNP and 6MWD (P <0.0001).

ATTR-CM, transthyretin amyloid cardiomyopathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; mITT, modified ITT; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTR, transthyretin.

1. Rapezzi C, et al. *Nat Rev Cardiol.* 2010;7(7):398-408. 2. Ruberg FL & Maurer MS. *JAMA.* 2024;331(9):778-791. 3. Penchala SC, et al. *Proc Natl Acad Sci USA*. 2013;110:9992-9997. 4. Miller M, et al. *J Med Chem.* 2018;61: 7862-7876. 5. Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-142.

Methods

ATTRibute-CM:
study design, key eligibility criteria, and primary endpoint[1]



*Primary analysis assessed using the Finkelstein-Schoenfeld method.

mITT Population† (N=611)
(Acoramidis, n=409; placebo, n=202)
Participants with baseline eGFR ≥30 mL/min/1.73 m^2

Stage 4 CKD participants (N=21)
(Acoramidis, n=12; placebo, n=9)
Participants with baseline eGFR <30 mL/min/1.73 $m^{2‡}$

ITT Population (N=632)
(Acoramidis, N=421; placebo, N=211)
All randomized participants

- Incidence of all-cause mortality in the mITT and ITT populations was evaluated using Cox model; prespecified sensitivity analyses included stratified log-rank and Cochran-Mantel-Haenszel tests

†Efficacy set. ‡Cohort included 1 patient with eGFR <15 mL/min/1.73 m^2.
6MWD, 6-minute walk distance; ^{99m}Tc, technetium-labeled pyrophosphate or bisphosphonate; ATTR-CM, transthyretin amyloid cardiomyopathy; BID, twice daily; CKD, chronic kidney disease; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; mITT, modified ITT; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; WT, wild-type.
1. Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-142.

Baseline Characteristics of the mITT and the High-Risk Stage 4 CKD Populations

	ITT Population (N=632)			
	mITT Population (eGFR ≥30 mL/min/1.73 m²); N=611		High-Risk Stage 4 CKD Population (eGFR <30 mL/min/1.73 m²)*; N=21	
	Acoramidis n=409	Placebo n=202	Acoramidis n=12*	Placebo n=9
Mean (SD) age, years	77 (6.5)	77 (6.7)	79 (5.6)	80 (7.0)
Sex, n (%)				
Male	374 (91.4)	181 (89.6)	10 (83.3)	5 (55.6)
Female	35 (8.6)	21 (10.4)	2 (16.7)	4 (44.4)
NYHA Class, n (%)				
I	51 (12.5)	17 (8.4)	0 (0)	0 (0)
II	288 (70.4)	156 (77.2)	5 (41.7)	6 (66.7)
III	70 (17.1)	29 (14.4)	7 (58.3)	3 (33.3)
eGFR, mL/min/1.73 m², mean (SD)	62 (17.4)	63 (17.5)	26 (5.9)	26 (2.3)
NT-proBNP ≤3000 pg/mL, n (%)	268 (65.5)	133 (65.8)	4 (33.3)	3 (33.3)
NT-proBNP >3000 pg/mL, n (%)	141 (34.5)	69 (34.2)	8 (66.7)	6 (66.7)
Genetic status**, n (%)				
Wild type	370 (90.5)	182 (90.1)	10 (83.3)	9 (100.0)
Variant	39 (9.5)	20 (9.9)	2 (16.7)	0 (0)

*Cohort included 1 patient in acoramidis group with eGFR = 8 mL/min/1.73 m².

** From IXRS Stratification Factors

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; IXRS, interactive voice/web response system; mITT, modified ITT; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Acoramidis was Associated With Fewer Observed Deaths Than Placebo in Both eGFR Groups (≥30 and <30 mL/min/1.73 m²)

	mITT Population (eGFR ≥30 mL/min/1.73 m²) N=611		High-Risk Stage 4 CKD Population (eGFR <30 mL/min/1.73 m²) N=21		Overall Population (ITT) N=632	
	Acoramidis n=409	Placebo n=202	Acoramidis n=12	Placebo n=9	Acoramidis n=421	Placebo n=211
All-cause mortality, n (%)	79 (19.3)	52 (25.7)	5 (41.7)	5 (55.6)	84 (20.0)	57 (27.0)
Cox proportional hazard model Hazard Ratio (vs placebo) 95% CI *p* value	0.772 (0.542, 1.102) 0.1543		NA* NA* NA*		0.762 (0.524, 1.072) 0.1184	
Log-rank test	0.0754		NA*		0.0520	
Cochran-Mantel-Haenszel test	0.0569		NA*		0.0390	
Any TEAEs, n (%)	402 (98.3)	197 (97.5)	11 (91.7)	9 (100)	413 (98.1)	206 (97.6)

*Inferential analysis comparing two groups within the pts <eGFR may not be meaningful/feasible given the small sample size.

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat; mITT, modified ITT; NA, not available; TEAEs, treatment-emergent adverse events.

Conclusions

ATTRibute-CM is the first ATTR-CM outcomes study to include participants with eGFR <25 mL/min/1.73 m^2

In high-risk participants with **stage 4 CKD**, acoramidis treatment was associated with **25% relative risk reduction in deaths at Month 30** versus placebo, consistent with the observations in mITT population, and with no safety signals of potential clinical concern

In a prespecified sensitivity analysis applied to the ITT population (mITT + stage 4 CKD), acoramidis **significantly reduced all-cause mortality** (HR = 0.762; *p*=0.039, Cochran-Mantel-Haenszel test)

ATTR-CM, transthyretin amyloid cardiomyopathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ITT, intention-to-treat.

Thank you

Baseline Characteristics of the mITT, High-Risk Stage 4 CKD, and ITT Populations

	mITT Population (eGFR ≥ 30 ml/min/1.73 m²) N=611		High-Risk Stage 4 CKD Population (eGFR < 30 ml/min/1.73 m²) N=21		Overall Population (ITT) N=632	
	Acoramidis n=409	Placebo n=202	Acoramidis n=12	Placebo n=9	Acoramidis n=421	Placebo n=211
Mean (SD) age, years	77 (6.5)	77 (6.7)	79 (5.6)	80 (7.0)	77 (6.5)	77 (6.8)
Gender, n(%)						
Male	374 (91.4)	181 (89.6)	10 (83.3)	5 (55.6)	384 (91.2)	186 (88.2)
Female	35 (8.6)	21 (10.4)	2 (16.7)	4 (44.4)	37 (8.8)	25 (11.8)
NYHA Class, n(%)						
I	51 (12.5)	17 (8.4)	0 (0)	0 (0)	51 (12.1)	17 (8.1)
II	288 (70.4)	156 (77.2)	5 (41.7)	6 (66.7)	293 (69.6)	162 (76.8)
III	70 (17.1)	29 (14.4)	7 (58.3)	3 (33.3)	77 (18.3)	32 (15.2)
eGFR, ml/min/1.73 m², mean (SD)	62 (17.4)	63 (17.5)	26 (5.9)	26 (2.3)	61 (18)	61 (19)
NT-proBNP, ng/L, mean (SD)	2865 (2149.6)	2650 (1899.5)	N/A	N/A	2946 (2226)	2725 (1971)
NT-proBNP ≤3000 pg/mL, n(%)	268 (65.5)	133 (65.8)	4 (33.3)	3 (33.3)	N/A	N/A
NT-proBNP >3000 pg/mL, n(%)	141 (34.5)	69 (34.2)	8 (66.7)	6 (66.7)	N/A	N/A
Genetic Status, n(%)						
Wild type	370 (90.5)	182 (90.1)	10 (83.3)	9 (100.0)	380 (90.3)	191 (90.5)
Variant	39 (9.5)	20 (9.9)	2 (16.7)	0 (0)	41 (9.7)	20 (9.5)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.