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- Dr. Alexander is an advanced heart failure-trained cardiologist. He is also an Assistant Professor of Cardiovascular Medicine at Stanford University School of Medicine
- He specializes in the management of advanced heart failure and transplant cases, and sees a wide range of patients. He also has an active research laboratory, studying various forms of heart failure
- Dr. Alexander has expertise in diagnosing and treating transthyretin cardiac amyloidosis, a critical yet underdiagnosed cause of heart failure among African Americans and the elderly. He is conducting extensive research to enhance our understanding of this condition, with grant support from the National Institutes of Health and American Heart Association, among other sources

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ACORAMIDIS ACHIEVES EARLY REDUCTION IN CARDIOVASCULAR-RELATED DEATH OR HOSPITALIZATION IN TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM): RESULTS FROM THE ATTRibute-CM CLINICAL TRIAL

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REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Acoramidis is an investigational agent being studied in patients with ATTR-CM

LEARNING OBJECTIVE

- Understand the treatment effect of acoramidis on time to CV-related mortality or first CV-related hospitalization in patients with ATTR-CM

INTRODUCTION

- ATTR-CM is a progressive cardiomyopathy resulting in **substantial cardiovascular morbidity and mortality** and caused by the **destabilization of the TTR tetramer**[1,2]
- **Acoramidis** is a next-generation, investigational, **near-complete TTR stabilizer** (>90%) for the treatment of patients with ATTR-CM[3-5]
- **Acoramidis demonstrated a significant improvement in a 4-step primary hierarchical endpoint of** mortality, morbidity, and function in the phase 3 **ATTRibute-CM**[a] study[6]
- Acoramidis also demonstrated a **50% relative risk reduction in the cumulative frequency of CVH** compared with placebo over 30 months[3,6]

OBJECTIVE

To report the prespecified time-to-first-event (TTE) analysis for the composite of CVM or CVH based on adjudicated data using the Cox proportional hazards model

[a]ATTRibute-CM (NCT03860935)

ATTR-CM, transthyretin amyloid cardiomyopathy; CVH, cardiovascular-related hospitalization; CVM, cardiovascular-related mortality; TTR, transthyretin.

1. Rapezzi C, et al. Nat Rev Cardiol. 2010;7(7):398-408. 2. Ruberg FL, et al. *JAMA*. 2024;331(9):778-791. 3. Judge DP, et al. *J Am Coll Cardiol*. 2019;74(3):285-295. 4. Penchala SC, et al. *PNAS*. 2013;110(24):9992-9997. 5. Miller M, et al. *Med Chem*. 2018;61(17):7862-7876. 6. Gillmore JD, et al. *N Engl J Med.* 2024;390(2):132-142.

METHODS: ATTRIBUTE-CM STUDY DESIGN

KEY ELIGIBILITY CRITERIA

- Participants with diagnosed ATTR-CM (WT or variant)
- NYHA class I-III
- ATTR-positive biopsy or ^{99m}Tc scan
- Light-chain amyloidosis excluded if diagnosis by ^{99m}Tc

Screening and randomization

30-month primary endpoint[a]:
Hierarchal analysis consisting of ACM, cumulative frequency of CVH, CFB in NT-proBNP, and CFB in 6MWD

Acoramidis HCl 800 mg BID
N=421

Placebo BID
N=211

Efficacy assessment included 611 participants in the prespecified mITT population[a,b,c]

[a]Primary analysis assessed using the Finkelstein-Schoenfeld method. [b]Participants with baseline eGFR of ≥30 mL/min/1.73 m^2. [c]14.9% and 22.8% of patients receiving acoramidis or placebo, respectively, used tafamidis after Month 12 (median duration: ~11 months).

6MWD, 6-minute walk distance; ^{99m}Tc, technetium-labeled pyrophosphate or bisphosphonate; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; BID, twice daily; CVH, cardiovascular-related hospitalization; CVM, cardiovascular-related mortality; eGFR, estimated glomerular filtration rate; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; WT, wild-type.

Gillmore JD, et al. *N Engl J Med.* 2024;390(2):132-142.

METHODS: OUTCOMES

Time to Event Composite Endpoint

CVM
Any death due to a cardiovascular or undetermined cause as determined by the CEC up to the 30-month duration
- Receiving a heart transplant or a CMAD was treated as CVM

CVH[a]
Adjudicated as CV-related and non-elective by the CEC, including EOCI[b]

- Kaplan-Meier curves by treatment groups were plotted for time to CVM or first CVH
- Analyses were performed using stratified Cox proportional hazards model

[a]CVH was defined as a non-elective admission to an acute care setting for CV-related morbidity that resulted in a ≥24-hour stay. [b]An unscheduled medical visit of <24 hours due to heart failure.

ACM, all-cause mortality; CEC, clinical events committee; CMAD, cardiac mechanical assist device; CV, cardiovascular; CVH, cardiovascular-related hospitalization; CVM, cardiovascular-related mortality; EOCI, event of clinical interest.

Gillmore JD, et al. *N Engl J Med.* 2024;390(2):132-142.

BASELINE CHARACTERISTICS WERE COMPARABLE BETWEEN TREATMENT GROUPS

	mITT Population N=611	
	Acoramidis n=409	Placebo n=202
Mean age, years (SD)	77 (6.5)	77 (6.7)
Sex, n (%)		
Male	374 (91.4)	181 (89.6)
NYHA class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
eGFR, mL/min/1.73 m^2		
Mean (SD)	62 (17.4)	63 (17.5)
Median (IQR)	62 (49, 74)	61 (48, 74)
NT-proBNP, pg/mL		
Mean (SD)	2865 (2149.6)	2650 (1899.5)
Median (IQR)	2273 (1315, 3872)	2274 (1128, 3590)
Genetic status[a], n (%)		
Wild-type	370 (90.5)	182 (90.1)
Variant	39 (9.5)	20 (9.9)

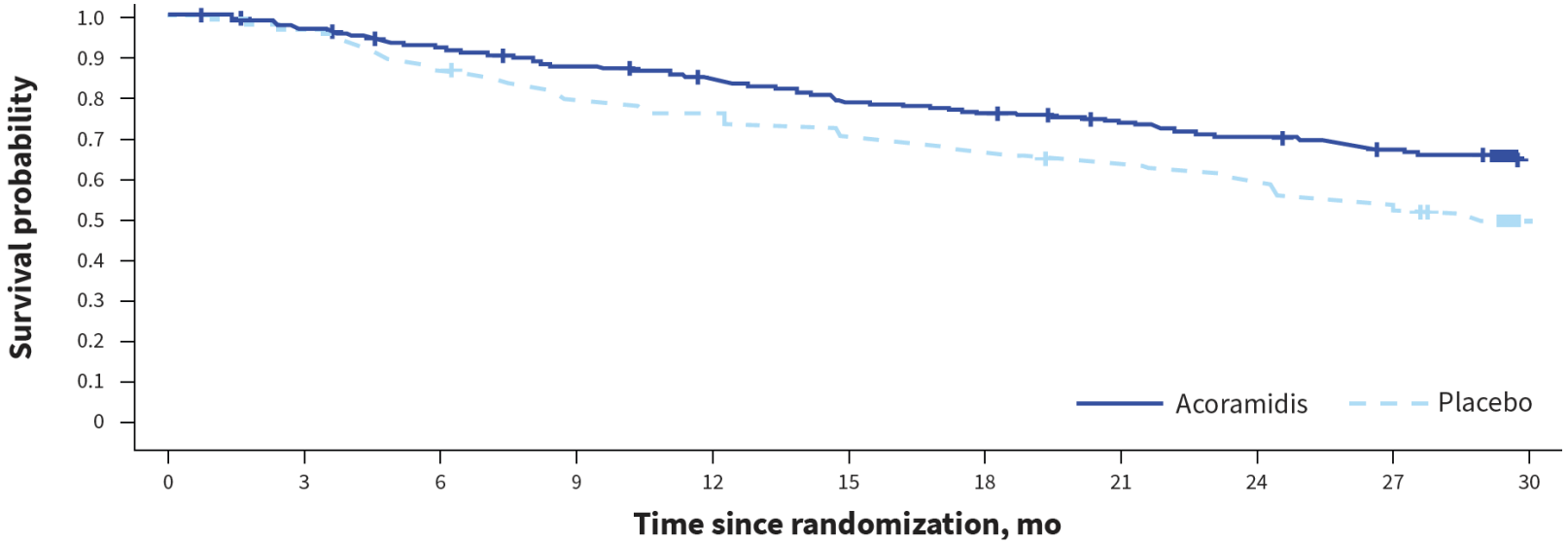
[a] From IXRS stratification factors

eGFR, estimated glomerular filtration rate; IXRS, interactive voice/web response system; IQR, interquartile range; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

ACORAMIDIS SIGNIFICANTLY IMPROVED CV OUTCOMES COMPARED WITH PLACEBO

KM curves separate early, at Month 3, and steadily diverge through Month 30

KM Curve for Time to CVM or First CVH Through Month 30 of Attribute-CM



Subjects remaining at risk (cumulative events)

Acoramidis	409 (0)	389 (18)	370 (36)	355 (50)	337 (66)	319 (84)	308 (94)	298 (102)	284 (116)	270 (128)	0 (136)
Placebo	202 (0)	191 (11)	172 (29)	159 (42)	152 (49)	143 (58)	135 (66)	129 (71)	121 (79)	108 (92)	0 (98)

Hazard ratio: 0.618[a]

95% CI: 0.475-0.803
p value = 0.0003

NNT to avoid CVM or first CVH over 30 months

7

15.2% absolute risk reduction and a **38.2% hazard reduction (p=0.0003)**

[a]Stratified Cox proportional hazards model includes treatment as an explanatory factor and baseline 6MWT as a covariate and is stratified by randomization stratification factors of genotype NT-proBNP level and eGFR level.
CV, cardiovascular; CVH, cardiovascular-related hospitalization; CVM, cardiovascular-related mortality; KM, Kaplan-Meier; NNT, number of patients needed to treat.

NO SAFETY SIGNALS OF POTENTIAL CLINICAL CONCERN WERE IDENTIFIED

Participants with ≥1 event	Acoramidis n=421	Placebo n=211
Any TEAEs, n (%)	413 (98.1)	206 (97.6)
TEAE with fatal outcome	60 (14.3)	36 (17.1)
TEAE leading to hospitalization	212 (50.4)	128 (60.7)
TEAE leading to study drug discontinuation	39 (9.3)	18 (8.5)
Any TESAEs, n (%)	230 (54.6)	137 (64.9)
TESAEs leading to study drug discontinuation	21 (5.0)	15 (7.1)
Severe TEAEs, n (%)[a]	157(37.3)	96 (45.5)

[a]As assessed by the investigator.
TEAE, treatment-emergent adverse event; TESAE, treatment-emergent severe adverse event.
Gillmore JD, et al. *N Engl J Med.* 2024;390(2):132-142.

CONCLUSIONS

Acoramidis treatment resulted in **an early and significant reduction in the composite endpoint of CVM or first CVH** in patients with ATTR-CM

To our knowledge, early separation of KM curves at 3 months represents the most **rapid clinical benefit** on the composite endpoint of CVM and CVH outcomes

Please visit the poster titled "Acoramidis Achieves Early Reduction in Cardiovascular Death or Hospitalization in Transthyretin Amyloid Cardiomyopathy (ATTR-CM): Results from the ATTRibute-CM Clinical Trial" [Poster # B-261]

ATTR-CM, transthyretin amyloid cardiomyopathy; CVH, cardiovascular-related hospitalization; CVM, cardiovascular-related mortality; KM, Kaplan-Meier.

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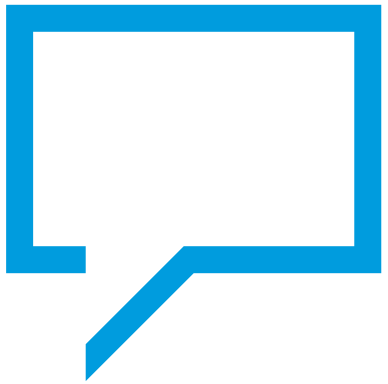
QUESTIONS & ANSWERS



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