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TREATMENT-RELATED EARLY INCREASE IN SERUM TTR IS ASSOCIATED WITH LOWER CARDIOVASCULAR HOSPITALIZATION IN ATTR-CM: INSIGHTS FROM ATTRibute-CM

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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 relationship between change in serum TTR and subsequent risk of first CVH in patients with ATTR-CM receiving a TTR stabilizer

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

BACKGROUND

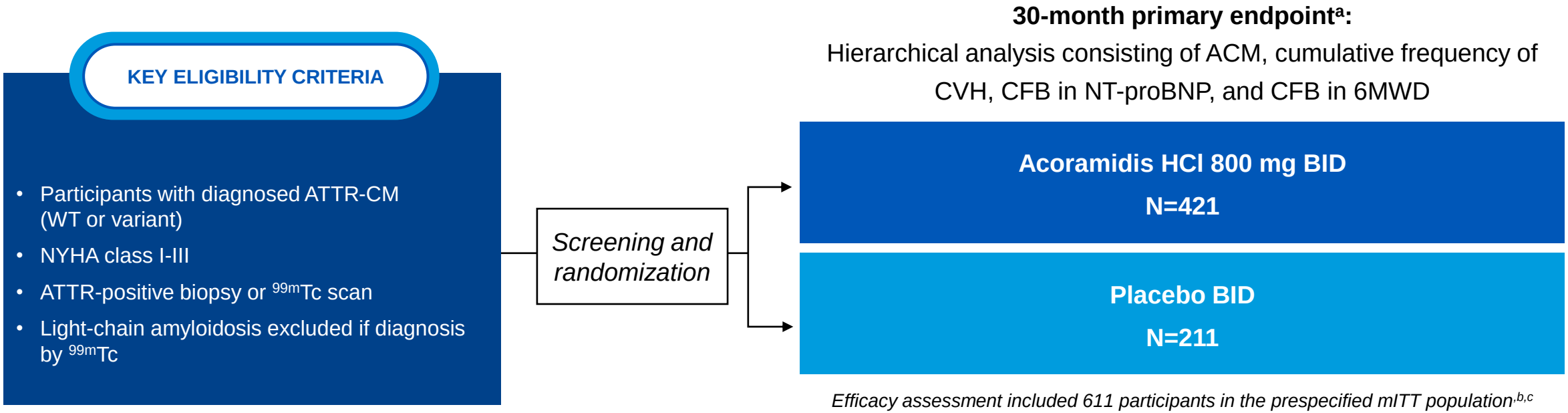
- Patients with **ATTR-CM can have lower circulating TTR levels**, which are associated with **worsening of cardiac function and increased risk of CVM**[1-3]
- **Acoramidis** is a next-generation, investigational, **TTR stabilizer**[4,5] that achieved near-complete (> 90%) stabilization and demonstrated robust clinical efficacy vs placebo in a pivotal phase 3 study, ATTRibute-CM[6]*
- **Acoramidis treatment resulted in a 50% reduction in the cumulative frequency of CVH** compared with placebo over 30 months, with a positive treatment effect **observed as early as 3 months**[7]
- The association between change in serum TTR and first CVH has not previously been described

PURPOSE: To evaluate the association between change in serum TTR and first CVH in patients receiving acoramidis or placebo in the ATTRibute-CM study

*ATTRibute-CM (NCT03860935) met its 4-step primary hierarchical endpoint of mortality, CVH, change in NT-proBNP and 6MWD ($p<0.0001$) in the mITT population.
6MWD, 6-minute walk distance; ATTR-CM, transthyretin amyloid cardiomyopathy; CVH, cardiovascular-related hospitalization; CVM, cardiovascular mortality; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTR, transthyretin.

1. Hanson JLS, et al. *Circulation: Heart Fail*. 2018;11(2):1-9. **2.** Rapezzi C, et al. *Nat Rev Cardiol.* 2010;7(7):398-408. **3.** Ruberg FL, et al. *JAMA*. 2024;331(9):778-7912. **4.** Penchala SC, et al. *PNAS*. 2013;110:9992-9997. **5.** Miller M, et al. *J Med Chem*. 2018;61: 7862-7876. **6.** Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-142. **7.** Judge DP, et al. Presented at the American Heart Association Congress,11-13 November 2023, Philadelphia, PA, US.

METHODS: ATTRibute-CM STUDY DESIGN



[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; 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: STATISTICAL ANALYSES

- Efficacy analyses were conducted in the mITT population[a] (acoramidis, n=409; placebo, n=202)
- The CFB in TTR levels were analyzed using MMRM
- CVH was adjudicated as CV-related and non-elective, including EOCIs[b], by the CEC[c]
- Kaplan-Meier curves by treatment groups were plotted for time to first CVH
- Analyses were performed using stratified Cox proportional hazards model

[a]Participants with baseline eGFR of ≥30 mL/min/1.73 m^2. [b]An unscheduled medical visit of <24 hours due to heart failure. [c]CVH was defined as a nonelective admission to an acute care setting for CV-related morbidity that resulted in a ≥24-hour stay.
CEC, clinical events committee; CFB, change from baseline; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; EOCIs, events of clinical interest; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; TTR, transthyretin.

BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS WERE COMPARABLE BETWEEN THE TREATMENT GROUPS

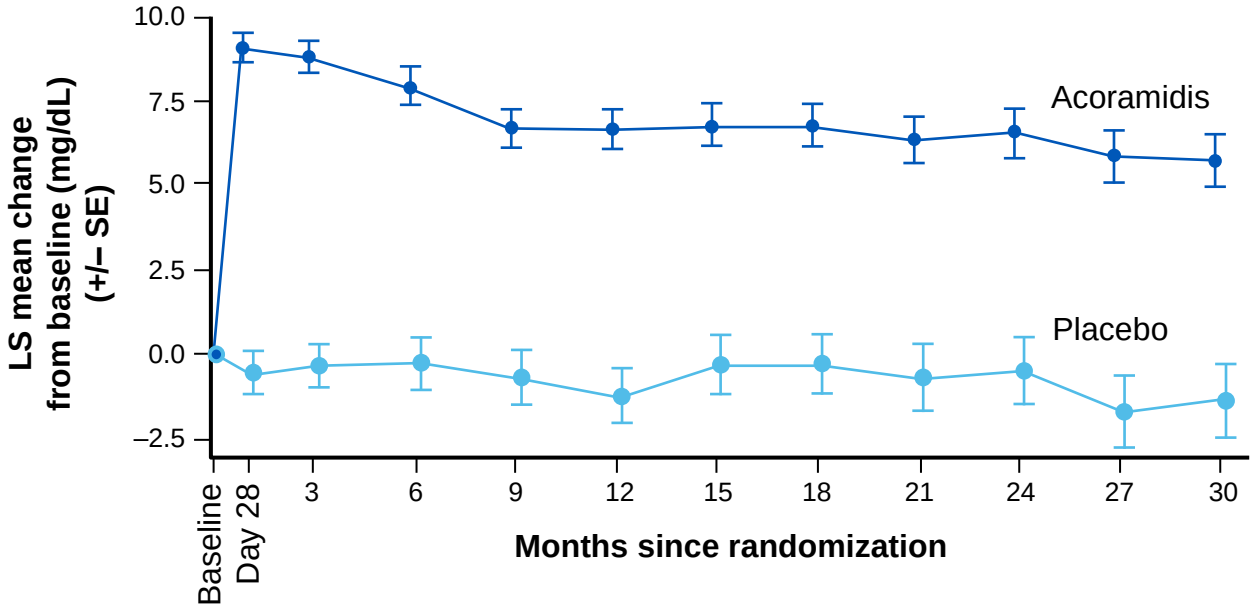
	mITT Population N=611	
	Acoramidis n=409	Placebo n=202
Mean age (SD), years	77 (6.5)	77 (6.7)
Sex, n (%)		
Male	374 (91.4)	181 (89.6)
NYHA class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
eGFR, mL/min/1.73 m^2		
Mean (SD)	62 (17.4)	63 (17.5)
Median (IQR)	62 (49, 74)	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; mITT, modified intent-to-treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

ACORAMIDIS TREATMENT ALONE INCREASED SERUM TTR LEVELS AT DAY 28, WHICH REMAINED STABLE THROUGH MONTH 30 WITH NO INCREASE IN SERUM TTR LEVEL OBSERVED FOR PLACEBO

Change in Serum TTR Level – MMRM (With J2R), mITT Population[1,a]



N												
Acoramidis	406	367	359	353	357	378	376	381	387	398	391	397
Placebo	199	178	177	173	177	188	185	192	195	194	187	197

- CFB in serum TTR level favored acoramidis at 30 months

  [LS mean difference: 7 mg/dL; 95% CI, 5.79-8.40; p<0.0001[1]]

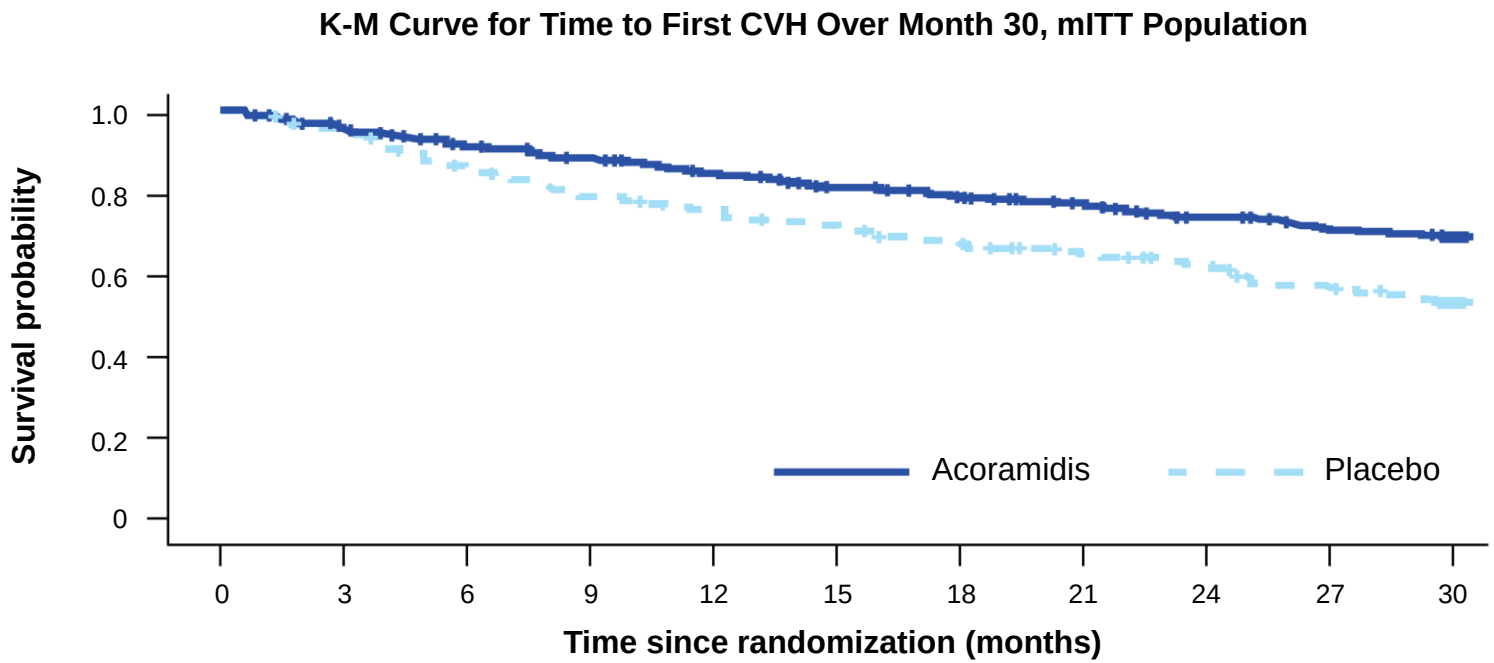
[a] The CFB in TTR level is analyzed using the MMRM with treatment group, visit, genotype (ATTRv-CM vs ATTRwt-CM), NT-proBNP level (≤3000 vs >3000), eGFR level (≥45 vs <45) and treatment group-by-visit interaction as factors, and baseline value as covariate. Graph displays modeled (not observed) effects.

ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, mutant/variant ATTR-CM; ATTRwt-CM, wild-type ATTR-CM; CFB, change from baseline; eGFR, estimated glomerular filtration rate; J2R, jump to reference; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTR, transthyretin.

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

ACORAMIDIS SHOWS SIGNIFICANT TREATMENT BENEFIT ON TIME TO FIRST CVH STARTING AT MONTH 3

K-M curves separate early, at Month 3, and steadily diverge through Month 30



Patients Remaining at Risk (Cumulative Events)

Acoramidis	409 (0)	380 (18)	349 (32)	332 (44)	311 (58)	292 (69)	277 (78)	265 (84)	249 (93)	234 (103)	0 (109)
Placebo	202 (0)	191 (10)	170 (28)	156 (41)	149 (47)	139 (56)	129 (63)	122 (66)	113 (72)	101 (81)	0 (86)

Hazard ratio: 0.601[a]

95% CI: 0.451-0.800
p value=0.0005

Number needed to treat to avoid first CVH over 30 months

7

[a]Stratified Cox proportional hazards model includes treatment as an explanatory factor and baseline 6MWD as a covariate, and is stratified by randomization stratification factors of genotype, NT-proBNP level and eGFR level as recorded in IXRS.
6MWD, 6-minute walk distance; CVH, cardiovascular-related hospitalization; IXRS, interactive voice/web response system; K-M, Kaplan–Meier.

ACORAMIDIS-MEDIATED TTR INCREASE AT DAY 28 IS ASSOCIATED WITH A LOWER RISK OF A FIRST CVH

	Acoramidis (n=409)	Placebo (n=202)
Patients with CVH, n (%)	109 (26.7)	86 (42.6)
Stratified Cox proportional hazards regression model of first CVH for each 1 mg/dL CFB in serum TTR at Day 28[a]		
HR (95% CI)	0.953 (0.919-0.989)	
p value	0.0115	

- **Each 1 mg/dL TTR increase** at Day 28 post-therapeutic intervention **was associated with a 4.7% lower risk of a first CVH** over 30 months
- These observations are across the baseline TTR and treatment groups

[a]Calculated for all patients with Day 28 CFB TTR values. Stratified Cox proportional hazards model includes baseline 6MWD and CFB in TTR level at Day 28 as covariates and is stratified by treatment group and randomization stratification factors of genotype, NT-proBNP level, eGFR level as recorded in IXRS and baseline TTR group (≥20 vs. <20).
6MWD, 6-minute walk distance; CFB, change from baseline; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IXRS, interactive voice/web response system; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTR; transthyretin.

CONCLUSIONS

Acoramidis treatment **increases serum TTR levels** as early as Day 28[1]

Acoramidis **reduces time to first CVH by 40%**, with treatment benefit starting early, at Month 3

- CVH has been shown to be a predictor of mortality in undifferentiated heart failure[2]

To the best of our knowledge, this is the first analysis from a prospective study of the relationship between CFB in TTR and subsequent risk of first CVH in ATTR-CM

An early and greater increase in TTR at Day 28 is associated with a **lower risk of CVH** over 30 months

Please visit the poster titled "Treatment-Related Early Increase in Serum TTR is Associated With Lower Cardiovascular Hospitalization in ATTR-CM: Insights From ATTRibute-CM)," Poster B-262

ATTR-CM, transthyretin amyloid cardiomyopathy; CFB, change from baseline; CVH, cardiovascular-related hospitalization; TTR; transthyretin.

1. Gillmore JD, et al. *N Engl J Med*. 2024;390(2):132-142. 2. Bello NA, et al. *Circ Heart Fail.* 2014;7(4):590-595.

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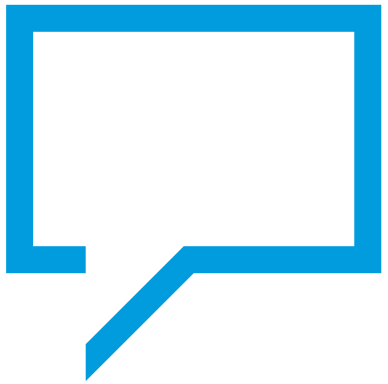
QUESTIONS & ANSWERS



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