Continuous Acoramidis Treatment Significantly Reduced Risk of All-Cause Mortality and Cardiovascular-Related Hospitalization Through Month 42 in Participants with Wild-Type and Variant Transthyretin Amyloidosis Cardiomyopathy

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Introduction

- ATTR-CM can develop due to the presence of a pathogenic TTR variant (ATTRv-CM) or misfolding of the wild-type transthyretin protein (ATTRwt-CM).[1,2] ATTRv-CM is typically associated with younger age of onset and faster progression than ATTRwt-CM[3-5]
- Acoramidis, an oral TTR stabilizer, achieves near-complete (≥ 90%) TTR stabilization, and is approved in the USA, Europe, Japan, and UK for treating ATTRv-CM or ATTRwt-CM in adults[6-9]
- Acoramidis reduced ACM or first CVH risk by 36% and annual CVH frequency by 50% through Month 30 versus placebo[10,11]
- In the OLE, continuous acoramidis treatment led to risk reductions of 36% in ACM, 43% in ACM/first CVH, and 47% in first CVH through Month 42 versus switching from placebo to acoramidis[12]

OBJECTIVE:
To assess the effects of continuous acoramidis treatment through Month 42 on ACM and CVH in participants with ATTRv-CM or ATTRwt-CM compared to 30 months of placebo followed by acoramidis through Month 42

ACM, all-cause mortality; ATTR-CM, TTR amyloid cardiomyopathy; CVH, cardiovascular-related hospitalization; CVM, cardiovascular mortality; OLE, open-label extension; TTR, transthyretin.

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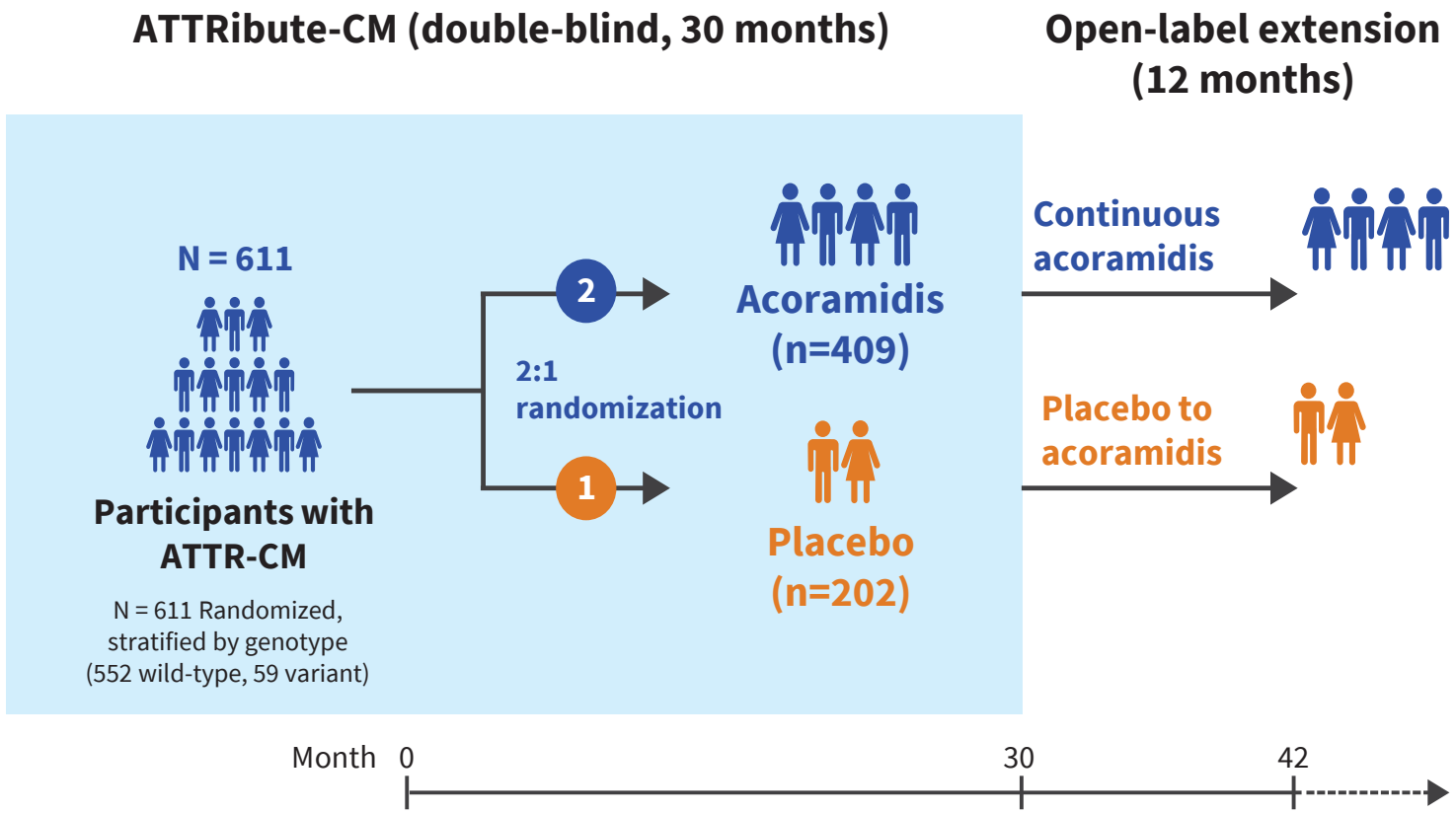
ATTRibute-CM and OLE Study Design



Outcomes analyzed by Genotype through Month 42 (30 months ATTRibute-CM + 12 months OLE)[a,b]:

- Time to first event for ACM[c]
- ACM or first CVH[d]
- First CVH

[a]For this study. [b]Time-to-event analyses used a stratified Cox proportional hazards model. Forest plots for HRs and associated 95% CIs by genotype used stratified Cox models with baseline 6MWD, treatment, genotype subgroup, and treatment by genotype interaction stratified by NT-proBNP and eGFR at randomization [c]ACM was defined as death due to any cause, receipt of a cardiac mechanical assist device placement, or receipt of a heart transplant. [d]CVH was defined as a non-elective admission to an acute care setting for cardiovascular-related morbidity 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.
6MWD, 6-minute walk distance; mITT, modified intent-to-treat; R, randomized; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Baseline Characteristics at Randomization in ATTRibute-CM Were Mostly Similar

Participant characteristics[a]	ATTRv-CM[b] (n = 59)		ATTRwt-CM[b] (n = 552)	
	Acoramidis n = 39[c]	Placebo n = 20[c]	Acoramidis n = 370[c]	Placebo n = 182[c]
Mean age, years (SD)	73.9 (7.60)	71.2 (7.84)	77.7 (6.25)	77.6 (6.32)
Male, n (%)	33 (84.6)	14 (70.0)	341 (92.2)	167 (91.8)
Duration of ATTR-CM, mean years (SD)	1.3 (1.06)	1.5 (1.07)	1.2 (1.22)	1.1 (1.21)
NYHA class, n (%)				
I	2 (5.1)	1 (5.0)	49 (13.2)	16 (8.8)
II	35 (89.7)	16 (80.0)	253 (68.4)	140 (76.9)
III	2 (5.1)	3 (15.0)	68 (18.4)	26 (14.3)
sTTR level, mean mg/dL (SD)	17.8 (5.12)	17.2 (5.22)	23.5 (5.34)	24.3 (5.75)
NT-proBNP, median pg/mL (IQR)	2326.0 (1312.0–4567.0)	2340.5 (1521.5–3534.0)	2264.5 (1315.0–3729.0)	2273.5 (1105.0–3590.0)
6MWD, mean meters (SD)	364.6 (94.93)	354.7 (97.07)	362.6 (104.49)	351.2 (93.74)
Concomitant tafamidis,[d] n (%)	4 (10.3)	4 (20.0)	57 (15.4)	42 (23.1)

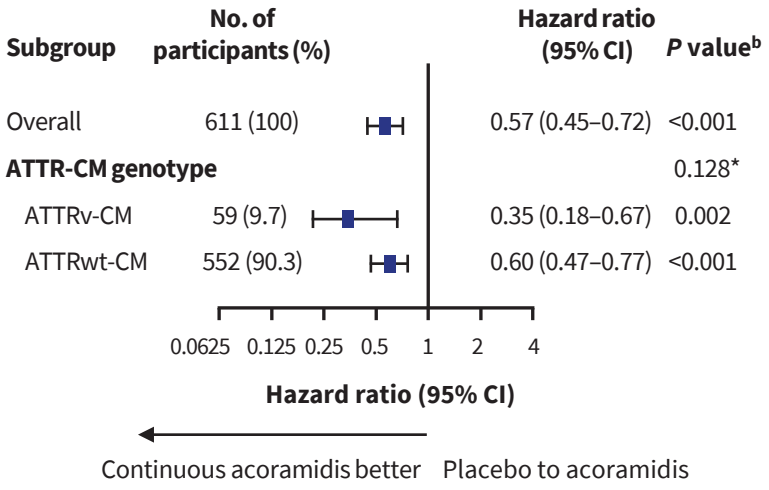
- The three most common ATTRv-CM variants were V142I (n = 35), I88L (n = 7), and T80A (n = 5)
- 380 of 611 participants in the mITT population entered the OLE
- On entry into the OLE, NT-proBNP and NYHA Class III were higher for placebo to acoramidis vs continuous acoramidis

[a]Data are for the full analysis set, which included the modified intention-to-treat population in ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy), which was defined as all participants who were randomized to acoramidis or placebo, received ≥1 dose of acoramidis or placebo, had ≥1 efficacy evaluation after baseline, and had a baseline estimated glomerular filtration rate (eGFR) of ≥30 mL/1.73 m^2. [b]Genotype based on information at randomization. [c]n values vary slightly for various characteristics based on available data. [d]Concomitant tafamidis was allowed after Month 12 of the double-blind period of ATTRibute-CM, but was prohibited during the OLE.
IQR = interquartile range; NYHA = New York Heart Association; SD = standard deviation; sTTR = serum transthyretin.

Continuous Acoramidis Reduced the Risk of ACM and CVH Through Month 42 Versus Placebo to Acoramidis Regardless of Genotype (mITT[a] Population)

Risk reductions through Month 42 with continuous acoramidis compared with placebo to acoramidis:

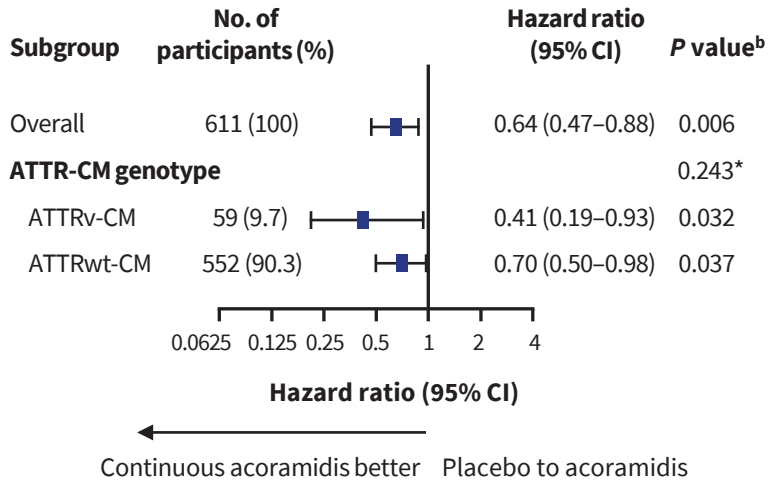
ACM/First CVH



ATTRv-CM: 65%

ATTRwt-CM: 40%

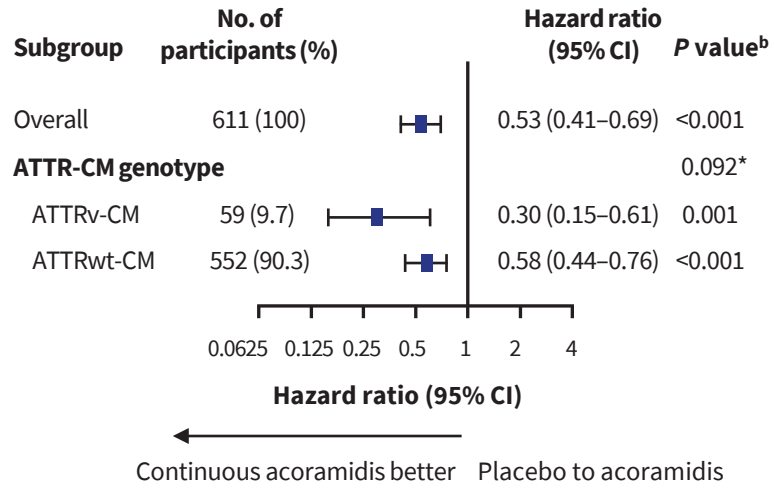
ACM



ATTRv-CM: 59%

ATTRwt-CM: 30%

First CVH



ATTRv-CM: 70%

ATTRwt-CM: 42%

[a]mITT analysis was continuous from the start of ATTRibute-CM into the OLE. [b]P-values with * are from testing the interaction of subgroup x treatment, and other p-values are for testing the treatment difference at a given value of subgroup variable.

Conclusions

In both ATTRv-CM and ATTRwt-CM, continuous acoramidis treatment through Month 42 of the ATTRibute-CM OLE was associated with consistently lower risks of ACM, ACM/first CVH, and first CVH compared with delayed initiation

No new clinically important safety issues were identified up to 42 months[a]

These findings highlight the long-term benefits of continuous acoramidis therapy regardless of variant or wild-type *TTR* genotypes, and underscore the importance of early treatment initiation

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See associated e-poster for more details.
[a]Data previously published in Judge DP, et al. *Circulation* 2025;151(9):601–611.