

Long-Term Durability of Acoramidis Efficacy in Transthyretin Amyloid Cardiomyopathy

Open-Label Extension of the ATTRIBUTE-CM Randomized Clinical Trial

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 Supplemental content

IMPORTANCE Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disorder caused by destabilization of serum transthyretin (sTTR). Acoramidis, an approved therapy that achieves near-complete ($\geq 90\%$) sTTR stabilization, demonstrated clinical benefit through month 30 in ATTRIBUTE-CM, which was incremental through month 42 in the open-label extension (OLE); however, the longer-term durability of outcomes has not been reported.

OBJECTIVE To evaluate the long-term efficacy and safety of acoramidis through month 54.

DESIGN, SETTING, AND PARTICIPANTS This OLE of the ATTRIBUTE-CM randomized clinical trial is an international, multicenter, ongoing OLE study. Data accumulated between October 2021 and April 2025 through month 24 of the OLE (month 54) are reported. Participants (aged 18-90 years) who completed ATTRIBUTE-CM and met the OLE eligibility criteria were invited to enroll in the OLE. Data were analyzed from May 2025 through November 2025.

INTERVENTIONS All OLE participants received open-label oral acoramidis, 800 mg, twice daily. Acoramidis recipients from ATTRIBUTE-CM continued therapy (continuous acoramidis) and placebo recipients switched to acoramidis (placebo to acoramidis).

MAIN OUTCOMES AND MEASURES The primary outcome was time to event for all-cause mortality (ACM), cardiovascular-related mortality (CVM), and first cardiovascular hospitalization (CVH), which was assessed for both groups. Biomarkers of disease progression (N-terminal pro-B-type natriuretic peptide [NT-proBNP]), sTTR, functional capacity (6-minute walk distance [6MWD]), and heart failure-related health status (Kansas City Cardiomyopathy Questionnaire–Overall Summary [KCCQ-OS] score) were analyzed.

RESULTS In ATTRIBUTE-CM, 632 participants were randomized to receive acoramidis ($n = 421$) or placebo ($n = 211$); mean (SD) age was 77.3 (6.6) years, and 62 participants (9.8%) were female. Overall, 389 participants enrolled in the OLE (263 in the continuous acoramidis group; 126 in the placebo-to-acoramidis group). Continuous acoramidis treatment reduced risks of ACM (hazard ratio [HR], 0.55; 95% CI, 0.42-0.74; $P < .001$) and CVM (HR, 0.51; 95% CI, 0.36-0.71; $P < .001$) through month 54, with consistent efficacy across all prespecified subgroups. Continuous acoramidis reduced time to first CVH (HR, 0.53; 95% CI, 0.42-0.69; $P < .001$) through month 54. Through month 54, continuous acoramidis stabilized increases in NT-proBNP, sustained higher sTTR levels, and stabilized KCCQ-OS score and 6MWD. Switching from placebo to acoramidis at month 30 was associated with stabilization of NT-proBNP and KCCQ-OS score and improvements in sTTR and 6MWD through month 54. No new long-term safety concerns were identified.

CONCLUSIONS AND RELEVANCE In this OLE of the ATTRIBUTE-CM randomized clinical trial, early and continuous acoramidis treatment resulted in sustained incremental reductions in ACM, CVM, and first CVH through month 54. These findings support the importance of early and continuous long-term treatment with acoramidis in ATTR-CM.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: [NCT04988386](https://clinicaltrials.gov/ct2/show/study/NCT04988386)

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Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease characterized by transthyretin (TTR) destabilization, which misfolds and deposits amyloid fibrils in the heart.¹⁻³ This process leads to heart failure, impaired quality of life, a greater cardiovascular hospitalization (CVH) burden, and premature death.²⁻⁵

Acoramidis, an oral TTR stabilizer, achieves near-complete ($\geq 90\%$) TTR stabilization and is approved in the US, Europe, Japan, and the United Kingdom for the treatment of wild-type or variant ATTR-CM (ATTRv-CM) in adults.⁶⁻⁹ In the phase 3 ATTRIBUTE-CM randomized clinical trial (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy, [NCT03860935](#)) and its open-label extension ([OLE], [NCT04988386](#)), participants with ATTR-CM who received acoramidis for 42 months had lower risks of all-cause mortality (ACM), cardiovascular-related mortality (CVM), and CVH than those who switched from placebo to acoramidis.^{5,10,11} Continuous acoramidis treatment through month 42 stabilized the rise in N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations and reduced the decline in heart failure-related health status and functional decline, as measured by the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score and 6-minute walk distance (6MWD), respectively, compared with those who switched from placebo to acoramidis.^{11,12}

The current analysis represents long-term systematic follow-up in a contemporary ATTR-CM population and evaluates the long-term safety of acoramidis, survival, biomarkers of disease progression, heart failure-related health status, and functional capacity through month 54 in the OLE of ATTRIBUTE-CM. Survival was examined across prespecified ATTR-CM subgroups, including women and those with ATTRv-CM.

Methods

Study Design and Participants

The study protocol of ATTRIBUTE-CM and its OLE is available in [Supplement 1](#), and the study design has been previously described (eMethods in [Supplement 2](#)).^{11,12} Participants who completed month 30 of ATTRIBUTE-CM and met OLE eligibility criteria were invited to enroll in the OLE, in which all participants received open-label acoramidis, 800 mg, twice daily. Concomitant tafamidis was not permitted in the OLE, and participants who had received concomitant tafamidis at any point in ATTRIBUTE-CM were required to discontinue it prior to entering the OLE. Participants who had previously received acoramidis for 30 months in ATTRIBUTE-CM continued to receive it in the OLE (continuous acoramidis group), and participants who had received placebo for 30 months in ATTRIBUTE-CM were switched from placebo to open-label acoramidis treatment (placebo-to-acoramidis group). This report contains data accumulated between October 2021 to April 2025 through month 24 of the OLE (month 54 since randomization in ATTRIBUTE-CM) for all OLE participants.

Key Points

Question Is long-term treatment with acoramidis in transthyretin amyloid cardiomyopathy associated with sustained clinical benefit through 54 months in the open-label extension of ATTRIBUTE-CM?

Findings Among 389 participants enrolled in the open-label extension of the ATTRIBUTE-CM randomized clinical trial, early and continuous acoramidis treatment was associated with sustained reductions in all-cause mortality, cardiovascular-related mortality, and first cardiovascular hospitalization, with consistent benefit across prespecified demographic and clinical subgroups. Biomarkers, functional capacity, and health status remained stable or improved, and no new long-term safety concerns were identified.

Meaning These findings support early and continuous acoramidis treatment to achieve long-term disease stabilization in transthyretin amyloid cardiomyopathy.

ATTRIBUTE-CM was conducted and its ongoing OLE is being conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocols were approved by an independent review board or ethics committee at each participating study site. All participants provided written informed consent. The Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guidelines were followed.

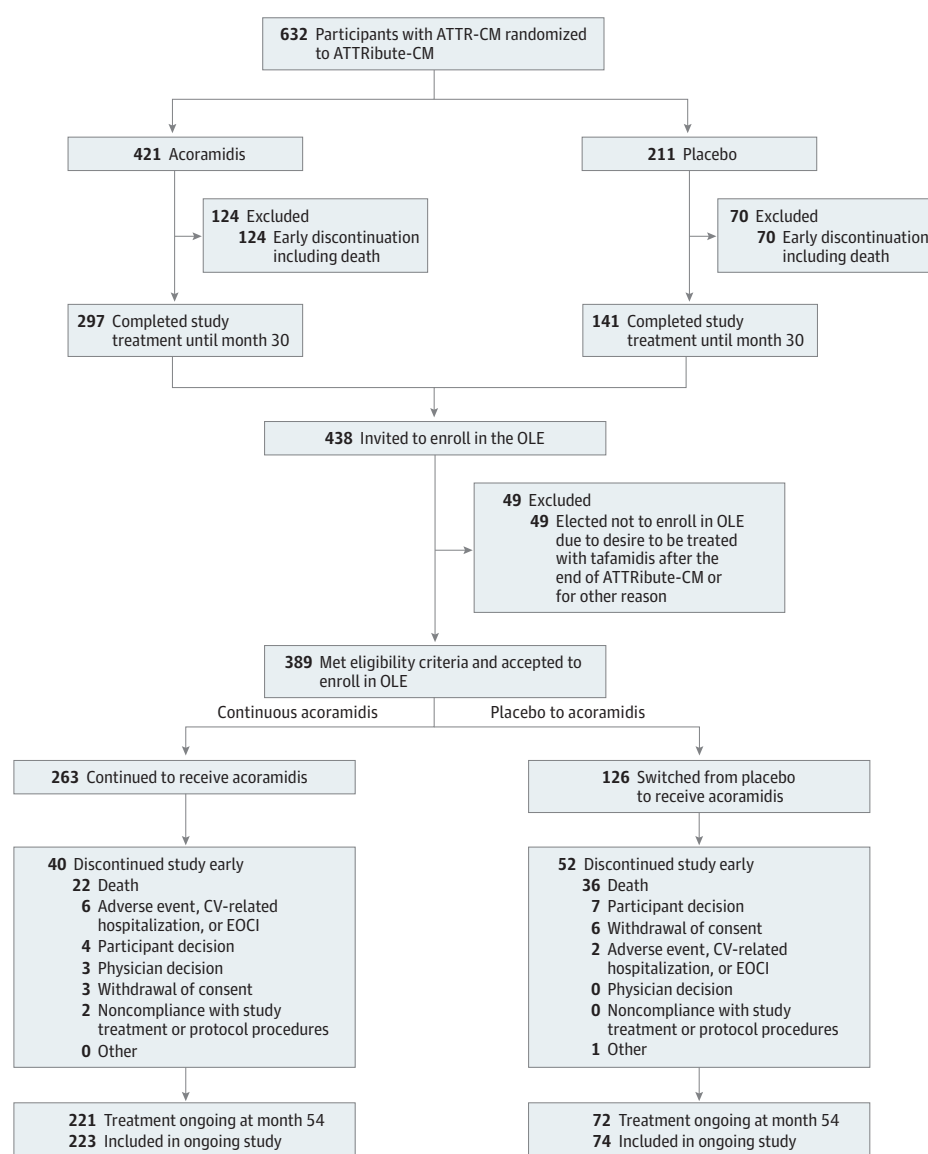
Outcomes

Analyses of ACM, CVM, and first CVH were conducted through month 54 in the full analysis set, which consisted of all participants in the ATTRIBUTE-CM modified intention-to-treat (mITT) population. The ATTRIBUTE-CM mITT population consisted of all randomized participants who had received at least 1 dose of acoramidis or placebo, had at least 1 efficacy evaluation after baseline, and had a baseline estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m² or higher. For the month 54 analyses, a data cut was conducted after all OLE participants had completed at least 24 months in the OLE (or had discontinued early), and observations were analyzed comparing the continuous acoramidis and placebo-to-acoramidis cohorts. Additional details of evaluation of ACM, CVM, and first CVH are provided in the eMethods in [Supplement 2](#).

Change from baseline in NT-proBNP levels, serum TTR (sTTR) levels, KCCQ-OS scores, and 6MWD up to month 54 are described based on observed values, with baseline being the value at the start (randomization) of ATTRIBUTE-CM. KCCQ-OS scores range from 0 to 100, with higher values indicating fewer symptoms and a better quality of life.

Safety was assessed by summarizing the frequency of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (AEs), treatment-related TEAEs, and severe TEAEs. An AE was considered an open-label acoramidis TEAE if it was not present before the first dose of open-label acoramidis or if it was present but increased in severity during the open-label acoramidis treatment-emergent period. Severity was assessed by the investigator.

Figure 1. CONSORT Flow Diagram



Statistical Analysis

Time to ACM, CVM, and first CVH analyses through month 54 were performed using a stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate. The model was stratified by genotype, NT-proBNP level, and eGFR as recorded at randomization.

Analyses were conducted to assess the geometric mean fold change from baseline in NT-proBNP levels from ATTRibute-CM through month 54, in addition to mean changes from baseline in sTTR levels, KCCQ-OS scores, and 6MWD, based on observed values. Results are presented with 95% confidence intervals or interquartile ranges. Two-sided $P < .05$ was taken to indicate nominal statistical significance. Statistical analysis was performed using SAS software version 9.4 or higher (SAS Institute).

Results

Participants

In ATTRibute-CM, 632 participants were randomized to receive acoramidis ($n = 421$) or placebo ($n = 211$) (Figure 1). The ATTRibute-CM mITT population included 611 participants (acoramidis, $n = 409$; placebo, $n = 202$). Baseline demographics and clinical characteristics have been described previously.^{11,12} The mean (SD) age was 77.3 (6.6) years, 62 participants (9.8%) were female, and 571 (90.3%) had wild-type ATTR-CM recorded at randomization. Baseline demographics and clinical characteristics were well matched between treatment groups (eTable 1 in Supplement 2).

Overall, 438 participants completed the ATTRibute-CM study (acoramidis, $n = 297$; placebo, $n = 141$),¹² and 389 par-

ticipants were enrolled in the OLE (continuous acoramidis, $n = 263$; placebo to acoramidis, $n = 126$) of 438 invited participants (Figure 1; 49 participants elected not to enroll in the OLE due to a desire to be treated with tafamidis after the end of ATTRIBUTE-CM or for other reasons). At the start of the OLE, a greater proportion of participants in the continuous acoramidis group had New York Heart Association (NYHA) class I or II (216 of 263 [82.1%] vs 79 of 126 [62.7%]), and mean (SD) sTTR levels were higher (32.8 [6.2] mg/dL vs 25.5 [6.5] mg/dL (eTable 1 in Supplement 2) compared with the placebo-to-acoramidis group.^{11,12}

The median (IQR) follow-up was 53.2 (52.8-53.5) months. At entry in the OLE, sodium-glucose cotransporter 2 (SGLT2) inhibitors were used by 53 among all participants (13.6%) (continuous acoramidis, 11.8%; placebo to acoramidis, 17.5%), and mineralocorticoid receptor antagonists (MRAs) were used by 132 participants (33.9%) of all participants (continuous acoramidis, 28.9%; placebo to acoramidis, 44.4%) (eTable 2 in Supplement 2). The drop-in rate for SGLT2 inhibitors during the OLE was 21.3% (56 participants initiating) in the continuous acoramidis group and 19.0% (24 participants initiating) in the placebo-to-acoramidis group. The drop-in rate for MRAs was 8.7% (23 participants initiating) in the continuous acoramidis group and 9.5% (12 participants initiating) in the placebo-to-acoramidis group (eTable 3 in Supplement 2). A total of 107 patients received tafamidis (61 of 409 [14.9%] in the acoramidis group and 46 of 202 [22.8%] in the placebo group), which represented 17.5% of the 611 patients who were included in the primary analysis.¹²

Time to ACM, CVM, and First CVH Through Month 54

ACM was reported in 107 of 409 participants (26.2%) in the continuous acoramidis group and in 88 of 202 participants (43.6%) in the placebo-to-acoramidis group through month 54 (Table 1). Continuous acoramidis treatment led to a 45% risk reduction in ACM (hazard ratio [HR], 0.55; 95% CI, 0.42-0.74; $P < .001$) vs placebo to acoramidis at month 54 (Figure 2A). CVM was reported in 76 of 409 participants (18.6%) in the continuous acoramidis group and in 68 of 202 participants (33.7%) in the placebo-to-acoramidis group through month 54 (Table 1). Continuous acoramidis treatment led to a 49% risk reduction in CVM (HR, 0.51; 95% CI, 0.36-0.71; $P < .001$) vs placebo to acoramidis at month 54 (Figure 2B).

Subgroup analyses of ACM and CVM showed that the survival benefit associated with continuous acoramidis treatment was consistent across all key demographic and clinical subgroups, including age, sex, race, genotype, NYHA class, and National Amyloidosis Centre (NAC) ATTR disease stage, with no evidence of treatment interaction, and was directionally consistent with the efficacy in the overall population (eFigure 1 in Supplement 2).

Time to first CVH was reported in 144 of 409 participants (35.2%) in the continuous acoramidis group and 115 of 202 participants (56.9%) in the placebo-to-acoramidis group through month 54. Continuous acoramidis treatment led to a 47% risk reduction in CVH (HR, 0.53; 95% CI, 0.42-0.69; $P < .001$) vs placebo to acoramidis at month 54 (eFigure 2 in Supplement 2).

Table 1. Summary of All-Cause Mortality (ACM) and Cardiovascular-Related Mortality (CVM) Events in the Continuous Acoramidis and Placebo-to-Acoramidis Groups at Month 54 (Full Analysis Set)

Event	Participants, No. (%)	
	Continuous acoramidis group (n = 409)	Placebo-to-acoramidis group (n = 202)
ACM ^a	107 (26.2)	88 (43.6)
CV-related death ^b	75 (18.3)	66 (32.7)
Heart failure	42 (10.3)	39 (19.3)
Undetermined death	16 (3.9)	14 (6.9)
Sudden cardiac death	14 (3.4)	11 (5.4)
Acute myocardial infarction	1 (0.2)	1 (0.5)
Other CV causes (eg, PE, DVT)	1 (0.2)	0
Stroke	1 (0.2)	0
CV procedures (caused by immediate complications)	0	1 (0.5)
Non-CV-related death	30 (7.3)	20 (9.9)
CMAD implantation	0	1 (0.5)
Heart transplant	1 (0.2)	1 (0.5)
CVM ^c	76 (18.6)	68 (33.7)

Abbreviations: CMAD, cardiac mechanical assist device; CV, cardiovascular; DVT, deep vein thrombosis; PE, pulmonary embolism.

^a ACM was defined as death from any cause, receipt of a heart transplant, or receipt of an implanted cardiac mechanical assist device.

^b CV-related death includes adjudicated CV-related death and death with undetermined cause per adjudication.

^c CVM includes any ACM adjudicated by the clinical events committee as due to a CV or undetermined cause.

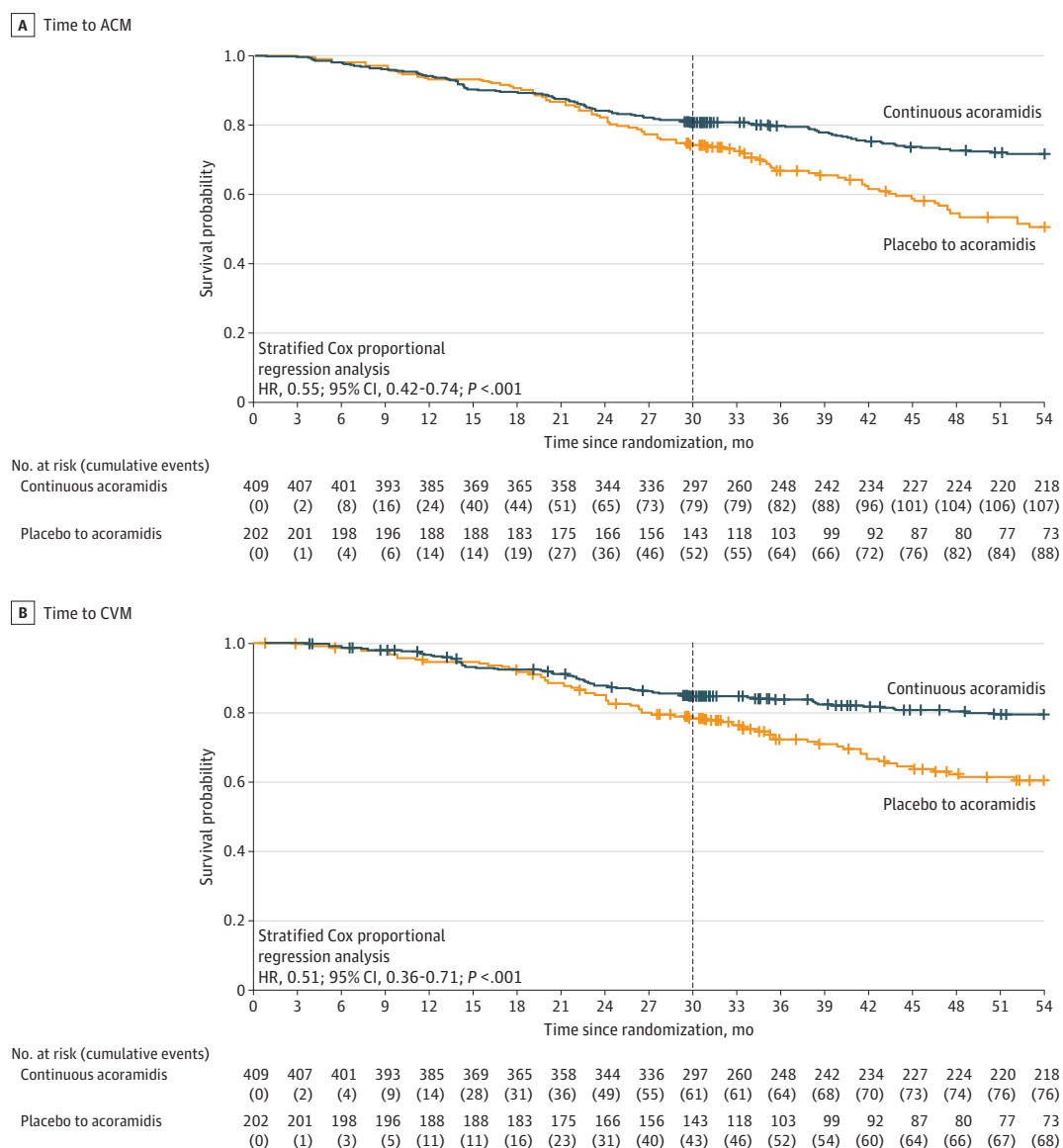
Biomarkers of Disease Progression, Heart Failure-Related Health Status, and Functional Capacity

Continuous acoramidis treatment stabilized NT-proBNP levels vs placebo in ATTRIBUTE-CM and in the OLE to month 54. Switching from placebo to acoramidis at month 30 stabilized NT-proBNP levels (Figure 3A). At month 54, the median (IQR) change from baseline in NT-proBNP levels was 57 (−572 to 918) pg/mL for continuous acoramidis and 1261 (253-2273) pg/mL for placebo to acoramidis (eTable 4 in Supplement 2), with percentage changes from baseline of 39.6% and 149.0%, respectively (Figure 3A). The geometric mean (SE) fold change from baseline in NT-proBNP levels was 1.10 (1.046) for continuous acoramidis and 2.00 (1.080) for placebo to acoramidis.

Acoramidis treatment increased sTTR levels vs placebo in ATTRIBUTE-CM, with an effect seen as early as day 28, and this increase was maintained through month 54 with continuous acoramidis. Placebo recipients who switched to acoramidis in the OLE demonstrated an increase in sTTR levels within the first month that were sustained through month 54 (Figure 3B). At month 54, the mean (SE) (95% CI) change from baseline in sTTR levels was 8.0 (0.39) (95% CI, 7.2-8.8) mg/dL for continuous acoramidis and 5.5 (0.87) (95% CI, 3.8-7.3) mg/dL for placebo to acoramidis, with percentage changes from baseline of 36.5% and 25.2%, respectively (Figure 3B; eTable 4 in Supplement 2).

KCCQ-OS scores were stable through month 54 in the continuous acoramidis group and declined slightly in the placebo-to-acoramidis group for 24 months in the OLE (Figure 3C). At month 54, the mean (SE) (95% CI) change from baseline in

Figure 2. Kaplan-Meier Curves for Time to All-Cause Mortality ([ACM], A) and Time to Cardiovascular-Related Mortality ([CVM], B) Through Month 54 (Full Analysis Set)



ACM was defined as death from any cause, receipt of a heart transplant, or receipt of an implanted cardiac mechanical assist device. CVM was defined as any death adjudicated as cardiovascular or of undetermined cause. The dotted lines at month 30 indicate the end of the ATTRIBUTE-CM study, after which all participants in the open-label extension received acoramidis. Analyses were performed using a stratified Cox proportional hazards model that included

treatment group as an explanatory factor and baseline 6-minute walk distance as a covariate. The model was stratified by the randomization factors of genotype, N-terminal pro-B-type natriuretic peptide level, and estimated glomerular filtration rate as recorded at randomization. HR indicates hazard ratio.

KCCQ-OS score was -4.8 (1.26) (95% CI, -7.3 to -2.3) for participants who received continuous acoramidis and -12.5 (2.2) (95% CI, -17.0 to -8.1) for placebo to acoramidis, with percentage changes from baseline of -4.7% and -15.8% , respectively (Figure 3C; eTable 4 in Supplement 2).

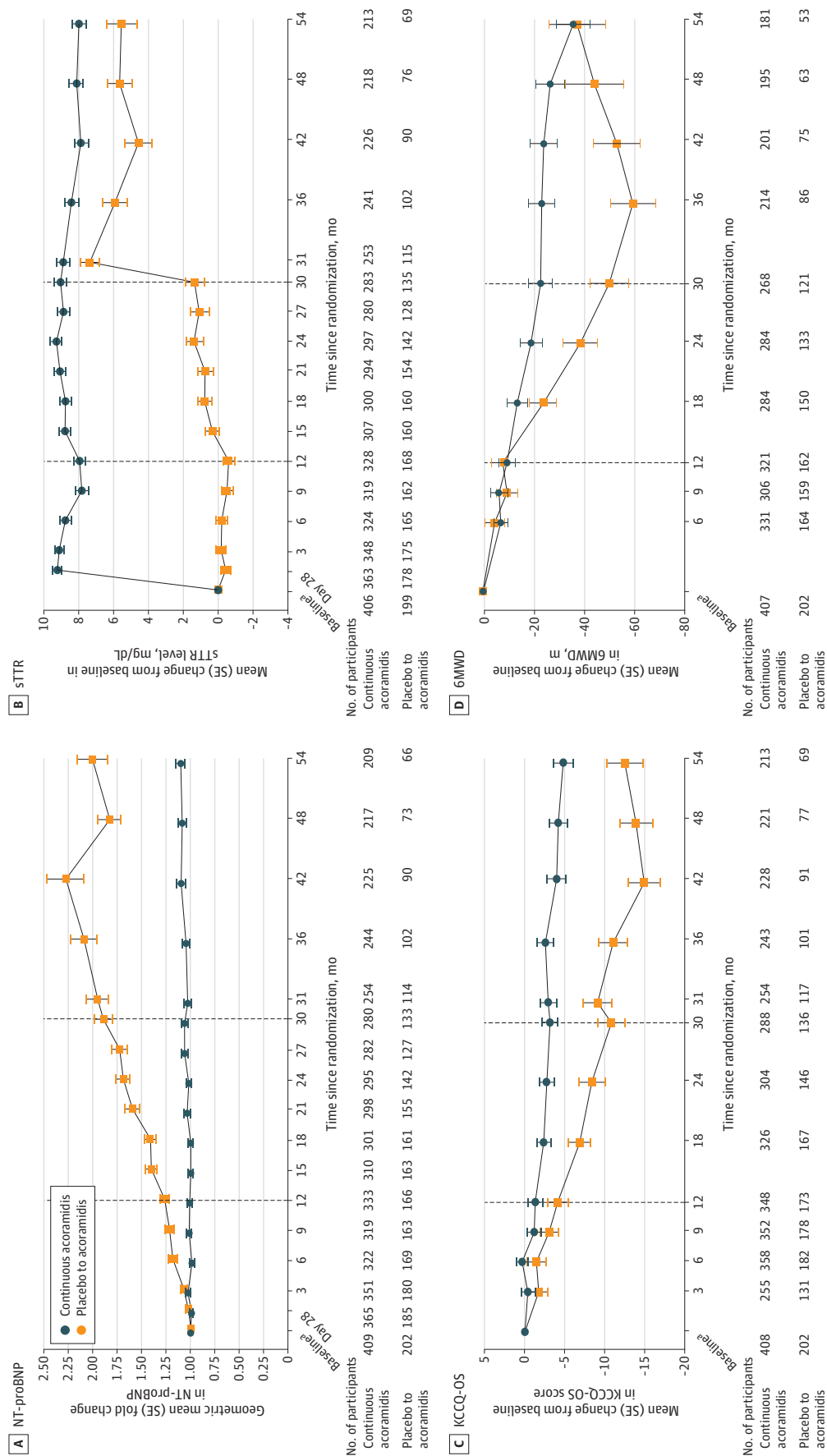
Continuous acoramidis treatment was associated with a slower decline in 6MWD up to month 30 compared with placebo; this trend continued between months 30 and 54 of the OLE (Figure 3D). Initiation of acoramidis at month 30 in the placebo-to-acoramidis group led to an improvement in 6MWD

through month 54. At month 54, the mean (SE) (95% CI) change from baseline in 6MWD was -35.7 (6.71) (95% CI, -49.0 to -22.5) m for continuous acoramidis and -37.3 (11.23) (95% CI, -59.8 to -14.8) m for placebo to acoramidis, with percentage changes of -9.3% and -10.1% , respectively (Figure 3D; eTable 4 in Supplement 2).

Safety

Safety outcomes for ATTRIBUTE-CM have been published previously and showed a similar frequency of AEs in the acor-

Figure 3. Line Graphs Showing Geometric Mean Fold Change From Baseline in N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) Levels (A) and Mean Change From Baseline in Serum Transthyretin (sTTR) Levels (B), Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ–OS) Scores (C), and 6-Minute Walk Distance (6MWD [D]) (Full Analysis Set)



*Baseline values are the last nonmissing assessment values obtained before the initiation of treatment in ATTRbute-CM.

The dotted lines at month 12 indicate the point after which tafamidis was permitted during the original ATTRbute-CM study. The dotted lines at month 30 indicate the end of the ATTRbute-CM study, after which all participants in the open-label extension received acoramidis.

Table 2. Summary of Treatment-Emergent Adverse Events (TEAEs) in the Continuous Acoramidis and Placebo-to-Acoramidis Groups During the Open-Label Extension (OLE) Period (OLE Study Entry to Month 54: OLE Full Analysis Set)

Event	Participants with ≥1 event, No. (%) [E] ^a		
	Continuous acoramidis group (n = 263)	Placebo-to-acoramidis group (n = 126)	Overall (n = 389)
Any TEAE ^b	248 (94.3) [1756]	119 (94.4) [1173]	367 (94.3) [2929]
TEAE with fatal outcome	27 (10.3) [34]	38 (30.2) [44]	65 (16.7) [78]
TEAE leading to hospitalization	122 (46.4) [295]	69 (54.8) [221]	191 (49.1) [516]
TEAE leading to study drug discontinuation	7 (2.7) [7]	3 (2.4) [4]	10 (2.6) [11]
TEAE leading to dose reduction	0	1 (0.8) [1]	1 (0.3) [1]
Any treatment-emergent SAE ^b	126 (47.9) [310]	75 (59.5) [245]	201 (51.7) [555]
Treatment-emergent SAE leading to study drug discontinuation	5 (1.9) [5]	2 (1.6) [2]	7 (1.8) [7]
Treatment-emergent SAE leading to dose reduction	0	0	0
Any treatment-related TEAE ^b	4 (1.5) [6]	6 (4.8) [9]	10 (2.6) [15]
Treatment-related treatment-emergent SAE	0	0	0
Severe TEAE ^c	90 (34.2) [219]	62 (49.2) [172]	152 (39.1) [391]

Abbreviations: AE, adverse event; SAE, serious adverse event.

^a No. represents the number of participants who experienced an event, and E represents the number of events.

^b An AE was considered an open-label acoramidis TEAE if the AE was not present before the first dose of open-label acoramidis or if it was present but increased in severity during the open-label acoramidis treatment-emergent period.

^c Severity as assessed by the investigator.

amidis and placebo groups. During the OLE period, TEAEs were reported in 367 of 389 participants (94.3%), with similar rates between the continuous acoramidis (248 of 263 [94.3%]) and placebo-to-acoramidis groups (119 of 126 [94.4%]) (Table 2). Overall, 10 participants (2.6%) experienced TEAEs leading to study drug discontinuation (continuous acoramidis, 2.7%; placebo to acoramidis, 2.4%); 7 participants (1.8%) experienced a treatment-emergent serious AE leading to study drug discontinuation (continuous acoramidis, 1.9%; placebo to acoramidis, 1.6%) (Table 2). The most frequently reported TEAEs in each treatment group during the OLE are provided in eTable 5 in Supplement 2. No new clinically important safety issues were identified in the OLE up to month 54.

Discussion

Here we report the long-term systematic follow-up of acoramidis treatment for ATTR-CM in a contemporary population integrating randomized and OLE data, providing important insights across ATTR-CM subpopulations. Early and continuous acoramidis treatment provided sustained and incremental reductions in ACM and CVM through month 54 compared with month 30 (ACM: HR, 0.77; 95% CI, 0.54-1.10; CVM: HR, 0.71; 95% CI, 0.48-1.05) and month 42 (ACM: HR, 0.64; 95% CI, 0.47-0.88; CVM: HR, 0.55; 95% CI, 0.39-0.79) (eFigure 2 in Supplement 2).^{5,11,13} These data support the hypothesis that earlier initiation of acoramidis may be associated with improved survival outcomes and are consistent with observations from other ATTR-CM therapies that demonstrated that treatment initiation in earlier phases of ATTR-CM may result in greater benefit.¹⁴

The long-term survival benefit associated with continuous acoramidis treatment appeared consistent across key demographic and clinical characteristics, including age, sex, race, genotype, NYHA class, and NAC ATTR disease stage, with no evidence of heterogeneity in the treatment effect. The observation of sustained efficacy in participants with more ag-

gressive disease, such as ATTRv-CM, and similar directional trends in historically inadequately characterized populations, such as women, has important clinical implications and supports treatment across ATTR-CM subpopulations.

Time to first CVH data were consistent with previously observed patterns in ATTRibute-CM and through month 42 of the OLE (HR, 0.53; 95% CI, 0.42-0.69).¹¹ An apparent stabilization in the HR for time to first CVH between months 42 and 54 of the OLE in both the continuous acoramidis and placebo-to-acoramidis groups may suggest that even patients with delayed initiation of acoramidis may experience lower risk in first CVH.

The natural course of ATTR-CM is characterized by progressive increases in NT-proBNP, as reflected in the placebo arm of ATTRibute-CM. Continuous acoramidis treatment was associated with durable stabilization of this key biomarker of disease progression. NT-proBNP is a well-established prognostic marker in heart failure and is incorporated into multiple ATTR-CM risk stratification scoring systems.¹⁵⁻¹⁷

Increased sTTR concentrations from baseline were sustained with continuous acoramidis treatment through month 54, and switching from placebo to acoramidis at month 30 resulted in a rapid and sustained increase. However, the magnitude of sTTR change from baseline was lower in the placebo-to-acoramidis group than in the continuous acoramidis group. Possible explanations for this may be the difference in clinical characteristics of the 2 groups at the time of acoramidis initiation, such as more advanced disease with poorer nutritional status in the placebo-to-acoramidis group. Taken together, the long-term stabilization of NT-proBNP and durable increase in sTTR observed with continuous acoramidis were associated with favorable modification of disease trajectory, consistent with sustained near-complete TTR stabilization achieved with acoramidis.

KCCQ-OS scores were preserved with continuous acoramidis treatment. Switching from placebo to acoramidis stabilized heart failure-related health status from months 30 through 54. Although previously reported observations to

month 42 showed little effect on KCCQ-OS score in the placebo-to-acoramidis group, improvements in KCCQ-OS score were observed in the placebo-to-acoramidis group to month 54, indicating that improvements in quality of life may occur even with later treatment initiation, although levels remained below those in the continuous acoramidis group. The shallow decline in KCCQ-OS score with acoramidis may be due in part to the natural consequences of aging.

Continuous acoramidis attenuated the decline in 6MWD observed with placebo, and participants who switched to acoramidis in the OLE demonstrated subsequent stabilization and improvement in functional capacity. By month 54, gains in 6MWD among participants who switched from placebo were comparable to those in participants receiving continuous acoramidis, suggesting that even delayed initiation of therapy may favorably modify ATTR-CM functional trajectory.

These results confirm the long-term tolerability and safety of acoramidis, with no long-term safety concerns identified during extended follow-up. A strength of this study is the extended efficacy follow-up in a contemporary cohort, which allowed assessment of long-term continuous acoramidis exposure compared with delayed initiation of acoramidis. Although later initiation of acoramidis provides benefit, the most pronounced effects occur with early and continuous treatment. Taken together, these findings confirm the importance of prompt diagnosis and treatment, while recognizing that patients presenting at an advanced stage may still benefit from therapy.¹⁸

Limitations

This study had several limitations. First, a subset of participants initiated treatment with concomitant tafamidis between months 12 and 30 in ATTRIBUTE-CM, and greater use was observed in the placebo group than in the acoramidis group. At OLE entry, SGLT2 inhibitor and MRA use was higher in the placebo-to-acoramidis group, with real-world evidence supporting their tolerability and effectiveness in ATTR-CM. During the OLE, drop-in rates of these medications were similar across both the continuous acoramidis and placebo-to-acoramidis groups. Viewed together, these imbalances in disease-specific therapy and heart failure medications consistently favored placebo and may have led to an underestimation of acoramidis efficacy.¹⁰ Second, because participants treated with acoramidis up to month 30 had reduced disease progression compared with those treated

with placebo, baseline characteristics in the OLE arms were not balanced (particularly for parameters linked to disease progression), which may have influenced the estimated treatment effect.¹¹ Third, the open-label design introduces inherent uncertainty regarding the interpretation of long-term safety outcomes, as there is no true control group for comparison.¹¹ As with other ATTR-CM clinical trials, ATTRIBUTE-CM and its OLE were not powered to assess treatment effects within individual subgroups, including racial and ethnic minorities, women, and those with ATTRv-CM. Finally, although this is one of the first reports of an extended follow-up through month 54 of a contemporary cohort, it may not encompass all potential patients with ATTR-CM. There is an important opportunity for future clinical trial and observational study designs to enhance our understanding of the rapidly evolving disease landscape through intentionally enriching enrollment of inadequately characterized populations and prospectively evaluating disease trajectories and treatment responses. Long-term analysis of time to first CVH should be interpreted with the limitation of the absence of a concurrent placebo group in the OLE, which may be further confounded by the placebo-to-acoramidis group receiving active therapy for 24 months. Finally, improvements in efficacy outcomes, such as the 6MWD and KCCQ-OS score in the placebo-to-acoramidis group, may be influenced by survivor bias, as participants with better functional status were more likely to remain in the study and contribute data, potentially overestimating the treatment benefit in later disease stages.

Conclusions

In this OLE of the ATTRIBUTE-CM randomized clinical trial, early and continuous acoramidis treatment resulted in sustained and incremental reductions in ACM and CVM and ATTR-CM disease stabilization through month 54 both in the overall population and across all prespecified subgroups, with no long-term safety concerns observed. Early and continuous acoramidis treatment also stabilized biomarkers of disease progression, heart failure-related health status, and functional capacity through month 54. These findings demonstrate the long-term, sustained clinical benefits of acoramidis in ATTR-CM and emphasize the need for early diagnosis followed by prompt treatment in patients with ATTR-CM.

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