Efficacy of Acoramidis on All-Cause Mortality and Cardiovascular Hospitalization in Transthyretin Amyloid Cardiomyopathy

Daniel P. Judge, MD,[a] Kevin M. Alexander, MD,[b,c] Francesco Cappelli, MD,[d] Marianna Fontana, MD, PhD,[e] Pablo Garcia-Pavia, MD, PhD,[f] Simon D.J. Gibbs, MD,[g,h,*] Martha Grogan, MD,[i] Mazen Hanna, MD,[j] Ahmad Masri, MD,[k] Mathew S. Maurer, MD,[l] Laura Obici, MD,[m] Prem Soman, MD, PhD,[n] Xiaofan Cao, PhD,[o] Ted Lystig, PhD,[o] Jean-François Tamby, MD,[o] Suresh Siddhanti, PhD,[o] Adam Castaño, MD, MS,[o] Leonid Katz, MD,[o] Jonathan C. Fox, MD, PhD,[o] Kenneth W. Mahaffey, MD,[c] Julian D. Gillmore, MD, PhD[e]

ABSTRACT

BACKGROUND Transthyretin amyloid cardiomyopathy (ATTR-CM) is an underdiagnosed chronic disease associated with progressive heart failure that results in impaired quality of life, repeated hospitalizations, and premature death. Acoramidis is a selective, oral transthyretin stabilizer recently approved by the U.S. Food and Drug Administration for the treatment of ATTR-CM. In a phase 3, randomized, double-blind study (ATTRibute-CM [Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy]), acoramidis was well tolerated and showed clinical efficacy in improving the primary endpoint, a hierarchical combination of all-cause mortality (ACM), cardiovascular-related hospitalization (CVH), N-terminal pro-B-type natriuretic peptide level, and 6-minute walk distance.

OBJECTIVES The goal of this study was to characterize the efficacy of acoramidis on ACM and CVH.

METHODS In ATTRibute-CM, participants with ATTR-CM were randomized 2:1 to receive acoramidis hydrochloride (800 mg twice daily) or placebo for 30 months. Efficacy analyses were conducted in the modified intention-to-treat population (participants with a baseline estimated glomerular filtration rate ≥30 mL/min/1.73 m^2). CVH and the composite of ACM or first CVH were plotted by using Kaplan-Meier curves and summarized with a stratified Cox proportional hazards model. The annualized frequency of CVH was analyzed by using a negative binomial regression model. Subgroup analyses were conducted for the composite of ACM or first CVH.

RESULTS Of the 632 participants randomized to treatment, 611 (97%) were included in efficacy analyses (acoramidis, n = 409; placebo, n = 202). Compared with placebo, acoramidis reduced the occurrence of the composite of ACM or first CVH (acoramidis, 35.9%; placebo, 50.5%; HR: 0.64; 95% CI: 0.50-0.83; $P = 0.0008$) and of first CVH (acoramidis, 26.7%; placebo, 42.6%; HR: 0.60; 95% CI: 0.45-0.80; $P = 0.0005$), with Kaplan-Meier curves separating at month 3 and continuing to diverge through month 30. Annualized frequency of CVH was reduced with acoramidis compared with placebo (acoramidis, 0.22; placebo, 0.45; relative risk ratio: 50%; 95% CI: 0.36-0.70; $P < 0.0001$). The efficacy of acoramidis on the composite of ACM or first CVH was consistent across subgroups. Acoramidis was well tolerated, with no safety signals of potential clinical concern identified.

CONCLUSIONS In participants with ATTR-CM, acoramidis reduced the composite of ACM or first CVH vs placebo, with an early effect driven by a reduction in CVH. (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy [ATTRibute-CM]; NCT03860935) (JACC. 2025;85:1003-1014) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by Editor Emeritus Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the [a]Division of Cardiology, Medical University of South Carolina, Charleston, South Carolina, USA; [b]Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Palo Alto, California, USA; [c]Stanford Center for Clinical Research, Stanford School of Medicine, Palo Alto, California, USA; [d]Tuscan Regional Amyloidosis Centre, Careggi University Hospital, Florence, Italy; [e]National Amyloidosis Centre, University College London, Royal Free Hospital, London, United Kingdom; [f]Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda and Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; [g]Victorian and Tasmanian Amyloidosis Service, Eastern

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2024.11.042

ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

ACM = all-cause mortality

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv-CM = variant transthyretin amyloid cardiomyopathy

ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy

CVH = cardiovascular-related hospitalization

EOCI = event of clinical interest

HFpEF = heart failure with preserved ejection fraction

mITT = modified intention-to-treat

MRA = mineralocorticoid receptor antagonist

NAC = National Amyloidosis Centre

NNT = number-needed-to-treat

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SGLT2 = sodium-glucose cotransporter 2

TEAE = treatment-emergent adverse event

TTR = transthyretin

IXRS = Interactive Voice/Web Response System

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a chronic progressive disease caused by destabilization and dissociation of transthyretin (TTR) protein tetramers, subsequent misfolding and aggregation of monomeric TTR into toxic amyloid precursors, and deposition leading to the accumulation of TTR amyloid fibrils in the heart.[1,2] This can result in progressive heart failure, reduced effort tolerance, impaired quality of life, and premature death.[1-4] Due to the progressive nature of ATTR-CM, both early and accurate diagnosis and timely initiation of treatment with rapid clinical benefits are essential.[2,5,6] In recent years, the ATTR-CM disease landscape has evolved considerably due to a confluence of factors: the adoption of noninvasive radionuclide cardiac amyloid imaging for confirming the diagnosis, improved heart failure management, availability of an effective targeted treatment (tafamidis), and engagement from professional societies and advocacy organizations to increase disease awareness among cardiologists and the broader medical community.[5-7] This has led to patients with ATTR-CM being diagnosed at earlier disease stages.[8-10] Despite these positive developments, ATTR-CM remains an underrecognized cause of heart failure leading to excess cardiovascular-related hospitalizations (CVHs) and mortality.[11,12]

SEE PAGE 1015

Acoramidis is an oral, selective TTR stabilizer for the treatment of ATTR-CM that inhibits the dissociation of tetrameric TTR.[13,14] It was rationally designed, as informed by human genetics and structural biology, to mimic the stabilizing effects of a disease-protective *TTR* gene variant *T119M* (also known as *p.Thr139Met*).[13,15] Structural biology studies show that acoramidis stabilizes TTR through 2 distinct mechanisms: an enthalpic-binding mode involving hydrogen bonding, as well as binding to both thyroxine-binding sites of the TTR tetramer.[15] In vitro and ex vivo assessments of acoramidis have shown TTR stabilization that is near-complete (≥90% across the entire dosing interval) and greater than that achieved with therapeutic concentrations of tafamidis.[14,16] In the phase 3 ATTRibute-CM (Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy; NCT03860935) study, acoramidis showed clinical efficacy compared with placebo for the primary outcome: a hierarchical 4-component analysis of all-cause mortality (ACM), the cumulative frequency of CVH, the change from baseline in N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, and the change from baseline in 6-minute walk distance (6MWD) over 30 months.[11] Acoramidis also showed a superior treatment effect compared with placebo for the prespecified secondary endpoint of the 2-component hierarchy of ACM and CVH.

The current paper reports prespecified secondary and post hoc analyses from the ATTRibute-CM study to further characterize the efficacy of acoramidis on the clinical outcomes of ACM and CVH. The goal of these prespecified supplementary analyses was to support clinicians in assessing study outcomes through more familiar methods, such as time-to-first-event analyses, Kaplan-Meier curves, and the number-needed-to-treat (NNT). In addition, an analysis of ACM and recurrent CVH is included to clarify the impact on disease burden for clinical outcomes by accounting for recurring events.

METHODS

STUDY DESIGN. Full details of the ATTRibute-CM study design have been previously published.[11] Briefly, this phase 3, randomized, multicenter, double-blind, placebo-controlled study enrolled men and women 18 to 90 years of age with an established diagnosis of chronic, stable, and symptomatic ATTR-CM; NYHA functional class I, II, or III; and either a wild-type or a variant TTR genotype.

Health, Melbourne, Victoria, Australia; [h]Epworth HealthCare, East Melbourne, Victoria, Australia; [i]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA; [j]Cleveland Clinic, Cleveland, Ohio, USA; [k]Division of Cardiology, Oregon Health & Science University, Portland, Oregon, USA; [l]Department of Medicine, Columbia University Irving Medical Center, New York, New York, USA; [m]Amyloidosis Research and Treatment Centre, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [n]Division of Cardiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; and the [o]BridgeBio Pharma, Inc, San Francisco, California, USA. *Dr Gibbs is now at BridgeBio Pharma, Inc, San Francisco, California, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received October 15, 2024; revised manuscript received November 21, 2024, accepted November 25, 2024.

ATTRibute-CM was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study was approved by the independent review board or ethics committee at each participating site. All participants provided written informed consent.

Participants were randomly assigned in a 2:1 ratio to receive acoramidis hydrochloride (800 mg) or matching placebo tablets administered orally twice daily for 30 months. Stratification was based on TTR genotype, NT-proBNP levels, and estimated glomerular filtration rate (eGFR) levels according to the National Amyloidosis Centre staging criteria.[17] Participants were permitted to initiate tafamidis, if available, as a concomitant medication after they had completed 12 months of the blinded study treatment.

All randomized participants received at least 1 dose of blinded study treatment. The efficacy analyses were conducted in the modified intention-to-treat (mITT) population, which consisted of all randomized participants who had at least 1 postbaseline efficacy evaluation and had a baseline eGFR ≥30 mL/min/1.73 m^2. Safety and tolerability were assessed in the safety population, which consisted of all randomized participants.

Sample size calculations have been previously described.[11] Briefly, sample size calculations were based on a 2-sided alpha of 0.04 using a total of 30 months of study data. Power calculations were based on the primary endpoint in ATTRibute-CM of a hierarchical combination of ACM and CVH over the 30-month treatment period. The test statistic for the combined endpoint was the Finkelstein-Schoenfeld test,[18] which was based on simulations of ACM and CVH and was shown in ATTR-ACT (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) to have >90% power with a total of 460 participants (after excluding 10% of subjects with baseline eGFR <30 mL/min/1.73 m^2) and a 2-sided alpha of 0.04.

EFFICACY ENDPOINTS. Participants were evaluated at 3-month intervals until month 30 during the double-blind treatment period. ACM was defined as death from any cause, receipt of a heart transplant, or receipt of an implanted cardiac mechanical assist device. Vital status for assessment of ACM at month 30 was obtained in all randomized study participants regardless of whether they remained on study treatment until month 30 or had discontinued treatment early. CVH was defined as a nonelective 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 <24 hours for the management of decompensated heart failure requiring treatment with an intravenous diuretic (from here referred to as an event of clinical interest [EOCI]). CVH events included all CVH (including EOCI) up to month 30 for participants who remained on study treatment until month 30, or up to 30 days after treatment discontinuation for participants who discontinued treatment early. Follow-up time for CVH events was censored at the date of last study treatment plus 30 days. Cause of death and suspected CVH events were adjudicated by an independent and blinded Clinical Events Committee. Cardiovascular-related mortality included death adjudicated as cardiovascular or of undetermined cause by the Clinical Events Committee, cardiac mechanical assist device implantation, and heart transplantation. Adjudicated events were the basis for efficacy analyses on ACM and CVH.

STATISTICAL ANALYSIS. Prespecified time-to-first-event analyses were performed by using a stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate and were stratified by the randomization factors of genotype, NT-proBNP level, and eGFR as recorded in the Interactive Voice/Web Response System (IXRS). No significant departures from the proportional hazards assumptions were observed for the composite endpoint of ACM or first CVH. Diagnostics for ACM alone, including an examination of both Schoenfeld and martingale residuals, suggested a possible violation of the proportional hazards assumption, particularly for the 6MWD covariate. Although the HR estimate is provided, to facilitate relevant comparisons, it should be interpreted with caution for the ACM alone model. Kaplan-Meier curves according to treatment group were plotted to visualize the time-to-first-event analyses for the composite endpoint of ACM or first CVH, and for the time-to-first CVH. To evaluate the impact of tafamidis initiation, sensitivity analyses were conducted on both the time to ACM or first CVH and on time to ACM by including a time-dependent covariate of tafamidis initiation status into the corresponding stratified Cox regression model. The annualized frequency of CVH was analyzed by using a negative binomial regression model with study treatment, randomization factors (ATTR-CM type, NT-proBNP level, and eGFR, as recorded in the IXRS), and an offset term equal to the log of the study duration for each participant included in the model. The NNT was calculated as 1/absolute risk reduction for the composite of ACM and first CVH, and for the annual frequency of CVH, both rounded up to the nearest whole

TABLE 1 Demographic and Clinical Characteristics of Participants at Baseline in ATTRibute-CM

	Acoramidis (n = 409)	Placebo (n = 202)	Total (N = 611)
Age, y	77.3 ± 6.5	77.0 ± 6.7	77.2 ± 6.6
Age category			
<65 y	12 (2.9)	9 (4.5)	21 (3.4)
≥65 to <78 y	186 (45.5)	92 (45.5)	278 (45.5)
≥78 y	211 (51.6)	101 (50.0)	312 (51.1)
Sex			
Male	374 (91.4)	181 (89.6)	555 (90.8)
Female	35 (8.6)	21 (10.4)	56 (9.2)
Race[a]			
White	358 (87.5)	179 (88.6)	537 (87.9)
Black or African American	19 (4.6)	10 (5.0)	29 (4.7)
Asian	10 (2.4)	3 (1.5)	13 (2.1)
Other	22 (5.4)	10 (5.0)	32 (5.2)
Transthyretin genotype[b]			
ATTRwt-CM	370 (90.5)	182 (90.1)	552 (90.3)
ATTRv-CM	39 (9.5)	20 (9.9)	59 (9.7)
Transthyretin variant			
V122I	23/37 (62.2)	12/19 (63.2)	35/56 (62.5)
T60A	3/37 (8.1)	2/19 (10.5)	5/56 (8.9)
E89Q	0/37	1/19 (5.3)	1/56 (1.8)
Other	11/37 (29.7)	4/19 (21.1)	15/56 (26.8)
NT-proBNP level, ng/L			
Median (Q1-Q3)	2,273.0 (1,315.0-3,872.0)	2,273.5 (1,128.0-3,590.0)	2,273.0 (1,240.0-3,729.0)
Mean ± SD	2,865.3 ± 2,149.6	2,650.1 ± 1,899.5	2,794.2 ± 2,071.2
eGFR, mL/min/1.73 m^2			
Median (Q1-Q3)	62.0 (49.0-74.0)	61.0 (48.0-74.0)	61.0 (49.0-74.0)
Mean ± SD	62.0 ± 17.4	62.5 ± 17.5	62.2 ± 17.4
NAC stage			
I	241 (58.9)	120 (59.4)	361 (59.1)
II	130 (31.8)	66 (32.7)	196 (32.1)
III	38 (9.3)	16 (7.9)	54 (8.8)
NYHA functional class			
I	51 (12.5)	17 (8.4)	68 (11.1)
II	288 (70.4)	156 (77.2)	444 (72.7)
III	70 (17.1)	29 (14.4)	99 (16.2)
Serum transthyretin, mg/dL			
Mean ± SD	23.0 ± 5.6	23.6 ± 6.1	23.2 ± 5.8
Total n	406	199	605

Values are mean ± SD, n (%), n/N (%), or median (Q1-Q3). Data are shown for the modified intention-to-treat population. [a]Race was reported by the participants. "Other" racial groups included America Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other, multiple races, and not reported. [b]Genetic status as recorded in the Interactive Voice/Web Response System.

ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; eGFR = estimated glomerular filtration rate; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

number. When risk reduction is discussed, it is defined as 1 minus the HR, or 1 minus the relative risk ratio, and is expressed as a percentage.

Prespecified subgroup analyses were performed for ATTR-CM genotype (variant ATTR-CM [ATTRv-CM] vs wild-type ATTR-CM [ATTRwt-CM]), baseline NT-proBNP level (≤3,000 pg/mL vs >3,000 pg/mL), baseline eGFR (<45 mL/min/1.73 m^2 vs ≥45 mL/min/1.73 m^2), age (<78 years vs ≥78 years), country of enrollment (United States vs rest of world), and NYHA functional class (I/II vs III). A post hoc subgroup analysis was performed by using National Amyloidosis Centre (NAC) ATTR stage (I vs II vs III). The NAC staging criteria are as follows[17]: stage I, NT-proBNP level ≤3,000 ng/mL and eGFR ≥45 mL/min/1.73 m^2; stage III, NT-proBNP level >3,000 ng/mL and eGFR <45 mL/min/1.73 m^2; the remainder of results with NT-proBNP and eGFR values are categorized as stage II, when both NT-proBNP and eGFR are not missing.

A post hoc analysis was conducted to evaluate the effect of acoramidis compared with placebo on the composite endpoint of ACM or recurrent CVH events using a negative binomial regression model in which treatment group, randomization stratification factors of genotype, NT-proBNP level, and eGFR from IXRS, and the offset term were used for the analysis. Relative risk ratios with 95% CIs were calculated. The incidence of ACM was assessed post hoc for participants with eGFR <30 mL/min/1.73 m^2.

We also report, post hoc, the drop-in rate during the study for 2 medication classes (mineralocorticoid receptor antagonists [MRAs] and sodium-glucose cotransporter 2 [SGLT2] inhibitors), defined as the percentage of participants with no medication from the class at baseline, who had a medication from the class initiated during the study after the first dose of blinded study treatment.

This paper includes several prespecified and post hoc analyses that are outside the scope of our alpha-controlled testing scheme covering the primary and key secondary endpoints.[11] P <0.05 are taken to indicate nominal statistical significance.

All analyses were performed by using SAS software version 9.4 or higher (SAS Institute Inc).

RESULTS

PARTICIPANT BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS. From April 2019 until October 2020, a total of 632 subjects underwent randomization (safety population) to receive acoramidis (n = 421) or placebo (n = 211) at 95 sites in 18 countries. The mITT population included 611 participants with an eGFR ≥30 mL/min/1.73 m^2: 409 in the acoramidis group and 202 in the placebo group. Baseline demographic and clinical characteristics of the mITT population were comparable between treatment groups (Table 1). The mean ± SD age of participants was 77.2 ± 6.6 years, and 90.8% were male. The reported mean time since diagnosis of ATTR-CM was 1.2

years (range: 0-10.1 years). Most participants had NYHA functional class I/II symptoms (512 of 611 [83.8%]) and NAC stage I/II ATTR-CM (557 of 611 [91.2%]). The median (Q1-Q3) duration of exposure to study treatment was similar in the acoramidis group (median: 29.5 months [Q1-Q3: 23.0-29.6 months]) and the placebo group (median: 29.4 months [Q1-Q3: 22.7-29.6 months]).

Tafamidis was initiated in 107 (17.5%) of 611 participants. In the acoramidis group, 61 (14.9%) of 409 participants received tafamidis, which was initiated after a median (Q1-Q3) of 17.8 months (Q1-Q3: 13.3-20.3 months). The median exposure time to concurrent study treatment and tafamidis was 11.4 months (Q1-Q3: 8.9-14.0 months). In the placebo group, tafamidis was initiated in 46 (22.8%) of 202 participants after a median of 16.1 months (Q1-Q3: 13.4-20.6 months) for a median exposure time of 9.9 months (Q1-Q3: 5.9-15.6 months).

At baseline, heart failure medications were taken by 621 (98.3%) of 632 participants in the safety population (Supplemental Table 1). MRAs were used by 34.0% (215 of 632) of participants (placebo: 72 of 211 [34.1%]; acoramidis: 143 of 421 [34.0%]), and SGLT2 inhibitors were used by 2.1% (13 of 632) of participants (placebo: 5 of 211 [2.4%]; acoramidis: 8 of 421 [1.9%]) at baseline.

TIME-TO-FIRST-EVENT ANALYSES. The composite endpoint of ACM or first CVH event over 30 months was reported in 147 (35.9%) of 409 and 102 (50.5%) of 202 participants in the mITT population treated with acoramidis and placebo, respectively, corresponding to a 14.6% absolute risk reduction and to an NNT of 7 to prevent ACM or first CVH over 30 months of treatment. The Cox regression analysis revealed a 36% risk reduction (HR: 0.64; 95% CI: 0.50-0.83; $P = 0.0008$). Kaplan-Meier curves for the time to ACM or first CVH for participants receiving acoramidis or placebo separated at month 3 and continued to steadily diverge through month 30 (**Central Illustration**, **Figure 1**). In a sensitivity analysis conducted with the addition of a time-dependent covariate for tafamidis, the HR of acoramidis for the risk of ACM or first CVH was similar at 0.65.

Over 30 months, ACM events were reported in 79 (19.3%) of 409 participants receiving acoramidis and 52 (25.7%) of 202 participants receiving placebo in the mITT population (HR: 0.77; 95% CI: 0.54-1.10; $P = 0.154$) (**Table 2**). The majority of ACM events (104 of 131 [79.4%]) were cardiovascular related. These were reported in 61 (14.9%) of 409 participants in the acoramidis group and 43 (21.3%) of 202 participants in the placebo group, corresponding to a 30% relative risk reduction with acoramidis treatment compared with placebo. Cardiac mechanical assist device implantation and heart transplantation occurred in 2 participants who received placebo (one had a cardiac mechanical assist device and one underwent a heart transplantation) and in no acoramidis-treated participants. For the subgroup of 21 participants with eGFR <30 mL/min/1.73 m^2 (excluded from the mITT population), ACM events were reported in 5 (41.7%) of 12 participants receiving acoramidis and 5 (55.6%) of 9 participants receiving placebo. In a sensitivity analysis conducted with the addition of a time-dependent covariate for tafamidis, the HR of acoramidis for the risk of ACM was unchanged at 0.77.

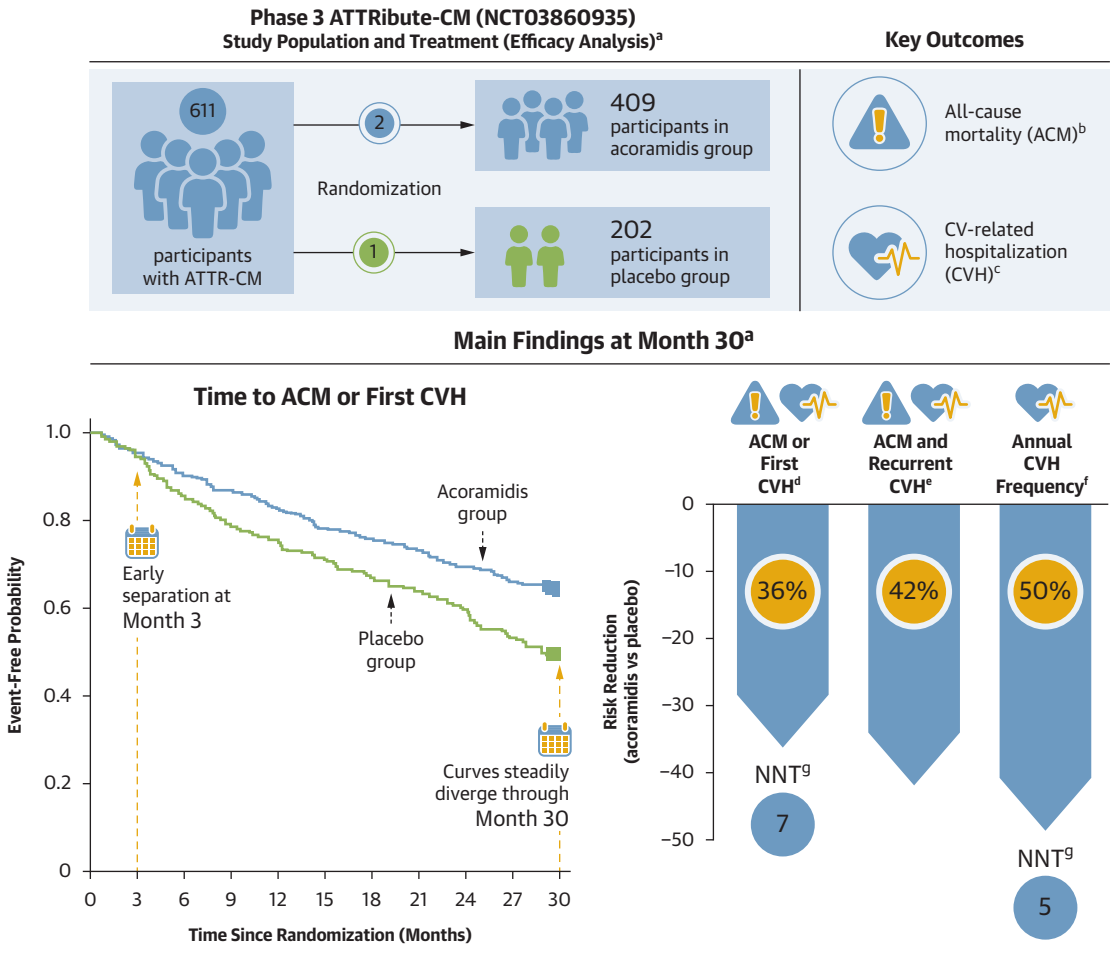
In total, 182 CVH events were reported by 109 (26.7%) participants receiving acoramidis, and 170 CVH events were reported by 86 (42.6%) participants receiving placebo in the mITT population (Supplemental Table 2, **Table 2**). The efficacy of acoramidis on CVH was observed for both CVH including and CVH excluding EOCIs. EOCIs were reported in 16 (3.9%) participants receiving acoramidis and 13 (6.4%) participants receiving placebo. The observed frequency of CVH per year was 0.29 for participants treated with acoramidis compared with 0.55 for those receiving placebo (Supplemental Table 2). The model-derived annualized frequency of CVH was significantly reduced with acoramidis (0.22 per year), compared with placebo (0.45 per year), corresponding to an absolute reduction of 0.23 per year, an NNT of 5 to prevent 1 CVH per year over 30 months of treatment, and a 50% reduction in risk ($P < 0.0001$) (**Table 2**).

The endpoint of first CVH event over 30 months corresponded to a 15.9% absolute risk reduction. The Cox regression analysis showed a 40% risk reduction (HR: 0.60; 95% CI: 0.45-0.80; $P = 0.0005$). Kaplan-Meier curves for the time to first CVH separated at month 3 and continued to steadily diverge through month 30 (**Figure 2**). The rate of CVH events at the time of separation of the Kaplan-Meier curves at month 3 was 4.6%, considering both treatment groups combined (total: 28 of 611; acoramidis: 18 of 409 [4.4%]; placebo: 10 of 202 [5.0%]).

Subgroup analyses for the composite of ACM or first CVH showed consistent efficacy favoring acoramidis across most participant subgroups of ATTR-CM genotype, NT-proBNP level, eGFR, age, country, NYHA functional class, and NAC stage (**Figure 3**).

ANALYSIS OF ACM AND RECURRENT CVH. Over 30 months, a total of 261 ACM and recurrent CVH events were reported in 409 acoramidis-treated participants compared with 222 total events reported in

CENTRAL ILLUSTRATION **Early Benefits of Acoramidis on All-Cause Mortality and Cardiovascular-Related Hospitalization in Transthyretin Amyloid Cardiomyopathy**



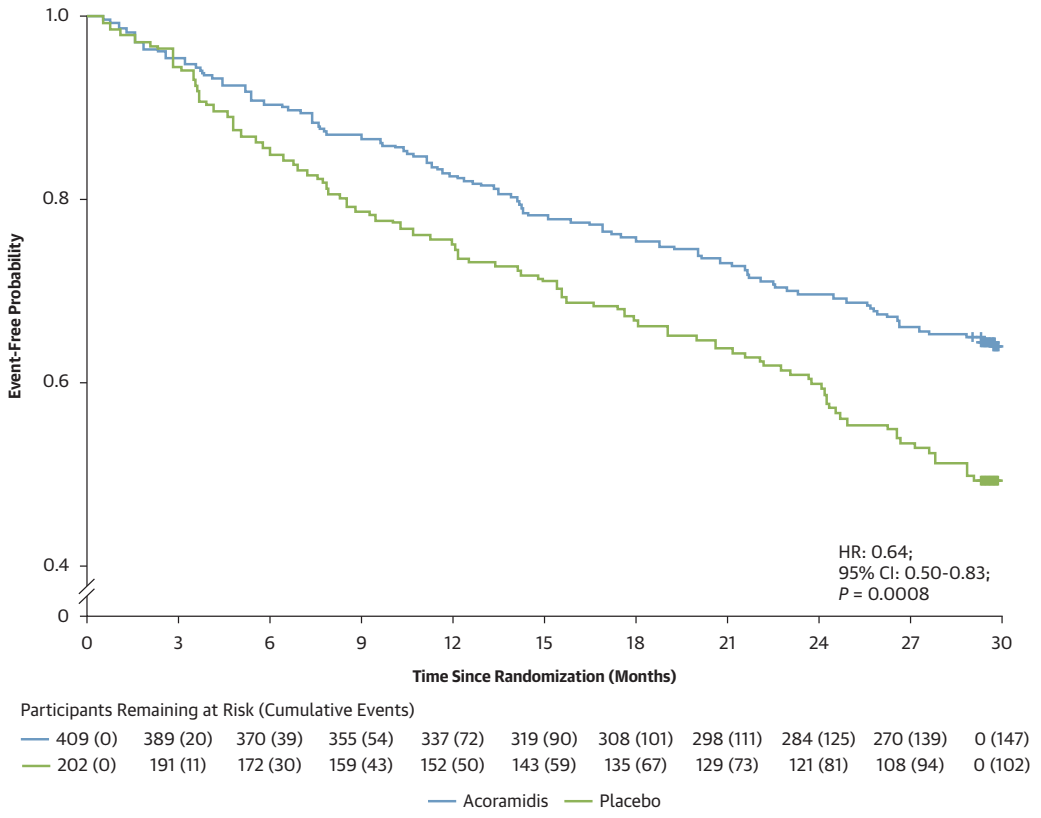
Judge DP, et al. JACC. 2025;85(10):1003-1014.

[a]Efficacy analyses were conducted in the modified intention-to-treat population (participants with one postbaseline efficacy evaluation and a baseline estimated glomerular filtration rate ≥30 mL/min/1.73 m^2). [b]Death from any cause, heart transplantation, or implantation of a cardiac mechanical assist device. [c]Nonelective admission to an acute care setting for cardiovascular (CV)-related morbidity that resulted in a ≥24-hour stay, or an unscheduled medical visit of <24 hours owing to heart failure and requiring treatment with intravenous diuretics. [d]Risk reduction is calculated as 1 - HR of the Kaplan-Meier analysis and is expressed as a percentage. [e]Analyzed using negative binomial regression. [f]Risk reduction is calculated as 1 - relative risk ratio of the annual cardiovascular-related hospitalization (CVH) frequency occurring in participants treated with acoramidis vs placebo and is expressed as a percentage. [g]Number-needed-to-treat (NNT) is the number of participants required to be treated for 30 months for one participant to experience a treatment benefit compared with placebo. ACM = all-cause mortality; ATTR-CM = transthyretin amyloidosis cardiomyopathy.

202 participants who received placebo. This corresponds to a total number of ACM and recurrent CVH events per participant observed of 0.64 (261 of 409) and 1.10 (222 of 202) with acoramidis and placebo, respectively. The negative binomial regression analysis showed that treatment with acoramidis led to a 42% risk reduction in ACM and recurrent CVH events over 30 months compared with placebo (relative risk ratio: 0.58; 95% CI: 0.43-0.79; $P = 0.0005$) (Table 2).

DROP-IN RATE OF SELECTED MEDICATIONS. The drop-in rate of MRAs during the study was 11.2% in the acoramidis group and 23.2% in the placebo group. The drop-in rate of SGLT2 inhibitors during the study

FIGURE 1 Kaplan-Meier Curve for the Time to the Composite Endpoint of ACM or First CVH Through Month 30



Data are shown for the modified intention-to-treat population. All-cause mortality (ACM) includes all-cause death, heart transplantation, and cardiac mechanical assist device implantation. Cardiovascular-related hospitalizations (CVHs) are those that were adjudicated as cardiovascular related and nonelective by a Clinical Events Committee, including events of clinical interest. The time to ACM or first CVH was analyzed by using a Cox proportional hazards model that included treatment as an explanatory factor and baseline 6-minute walk distance as a covariate, stratified by randomization factors of genotype, N-terminal pro-B-type natriuretic peptide, and estimated glomerular filtration rate.

was 8.3% in the acoramidis group and 13.3% in the placebo group (Supplemental Table 3).

SAFETY OUTCOMES. A summary of treatment-emergent adverse events (TEAEs) has been published previously.[11] In brief, the overall numbers of participants in the safety population who experienced a TEAE were similar between groups: 413 (98.1%) of 421 who received acoramidis and 206 (97.6%) of 211 who received placebo. Few TEAEs led to discontinuation of study treatment in either treatment arm (acoramidis, n = 39 [9.3%]; placebo, n = 18 [8.5%]). Cardiac failure was the most frequently reported TEAE in both treatment arms (acoramidis, n = 101 [24.0%]; placebo, n = 83 [39.3%]).

DISCUSSION

In the ATTRibute-CM study involving participants with ATTR-CM, treatment with acoramidis was associated with a 36% reduced risk for the composite of ACM or first CVH compared with placebo. These results correspond to an NNT of 7 for the prevention of ACM or first CVH over 30 months of treatment and complement the efficacy of acoramidis shown in the previously reported Finkelstein-Schoenfeld 2-component hierarchical analysis of ACM and CVH.[11]

The Kaplan-Meier curves for the composite of ACM or first CVH separated at month 3 and continued to diverge through month 30, with the initial separation driven by an early effect on CVH. The favorable trend

TABLE 2 Summary of ACM and CVH

	Acoramidis (n = 409)	Placebo (n = 202)
No. of participants with ACM and/or CVH events		
ACM or CVH	147 (35.9)	102 (50.5)
ACM[a]	79 (19.3)	52 (25.7)
Deaths[b]	79 (19.3)	50 (24.8)
CV-related deaths[c]	61 (14.9)	41 (20.3)
Non-CV-related deaths	18 (4.4)	9 (4.5)
Cardiac mechanical assist device	0 (0)	1 (0.5)
Heart transplantation	0 (0)	1 (0.5)
CV-related mortality[d]	61 (14.9)	43 (21.3)
CVH[e]	109 (26.7)	86 (42.6)
EOCI	16 (3.9)	13 (6.4)
CVH, excluding EOCI	101 (24.7)	79 (39.1)
Annualized frequency of CVH		
Frequency of CVH per year (95% CI)[f]	0.22 (0.18-0.28)	0.45 (0.35-0.58)
Relative risk ratio (95% CI) negative binomial regression	0.50 (0.36-0.70)[11]	
P Value	<0.0001	
No. of ACM and CVH events		
ACM and recurrent CVH[g]	261	222
ACM,[a]	79	52
CVH,[e,g]	182	170
EOCI	24	15
CVH, excluding EOCI	158	155
Total no. of ACM and recurrent CVH[g] events per participant	0.64	1.10
Relative risk ratio[h] (95% CI) negative binomial regression	0.58 (0.43-0.79)	
P Value	0.0005	

Values are n or n (%) unless otherwise indicated. Data are shown for the modified intention-to-treat population. [a]All-cause mortality (ACM) includes all-cause death, heart transplantation, and cardiac mechanical assist device implantation. [b]Cause of death indicated as per Clinical Events Committee (CEC) adjudication. [c]Cardiovascular (CV)-related death includes all deaths adjudicated by the CEC as CV or of undetermined cause. [d]CV-related mortality includes CV-related death, cardiac mechanical assist device, and heart transplantation. [e]CV-related hospitalizations (CVHs) are those that were adjudicated as CV related and nonelective by the CEC, including events of clinical interest (EOCI). Participants without a CVH event were censored at the earliest date of the last dose date + 30 days, day 907, the ACM date, or the last known alive date. [f]The annualized frequency of CVH was analyzed by using a negative binomial regression model. [g]In participants who discontinued treatment, CVH events were counted until 30 days after treatment discontinuation. [h]Relative risk ratio is calculated by (1 − relative risk ratio from the negative binomial regression analysis) × 100%.

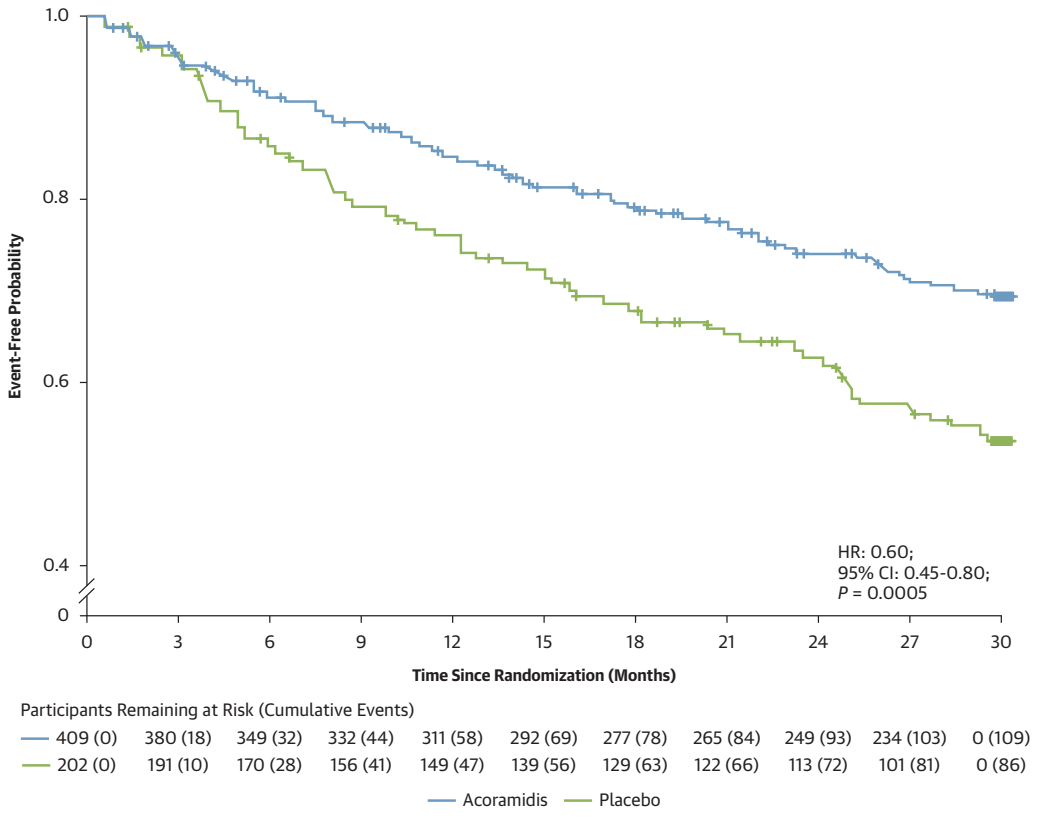
in reducing ACM at month 30 was driven by a 30% relative risk reduction in cardiovascular-related mortality observed with acoramidis treatment compared with placebo. The annual frequency of CVH was reduced by 50%, corresponding to an NNT of 5 to prevent 1 CVH per year over 30 months of treatment with acoramidis. We hypothesize that the large and early benefit on CVH with acoramidis may positively affect the quality of life of patients with ATTR-CM, as shown in ATTRibute-CM with the Kansas City Cardiomyopathy Questionnaire overall summary score favoring acoramidis relative to placebo.[11,19] In ATTRibute-CM, CVH included EOCIs, which were unplanned medical visits requiring treatment with an intravenous diuretic for the management of decompensated heart failure. EOCIs represented 11% of all CVH events reported during the study. The reduction in CVH with acoramidis treatment vs placebo was observed consistently for both types of CVH events (ie, CVH including EOCIs and CVH excluding EOCIs). Furthermore, the efficacy of acoramidis on CVH may have resulted in a lower drop-in rate of MRAs and SGLT2 inhibitors during the study in the acoramidis group compared with placebo.

The time to effect on ACM with acoramidis treatment vs placebo was longer than that observed for CVH. One hypothetical mechanism for this difference could be that the effects on CVH, which started at month 3, are related to the rapid stabilization in TTR (seen as early as day 28),[11] which prevents the formation and deposition of newly formed toxic amyloid precursors. The improvement in ACM observed from month 19 onward[11] may be driven by additional long-term effects of TTR stabilization on the amyloid fibril load already deposited in the heart.

The efficacy of acoramidis on the composite of ACM or first CVH was consistent across most subgroups, including those based on ATTR-CM genotype, age, baseline NT-proBNP level, baseline eGFR, and country. Patients at earlier ATTR-CM disease stages (NAC stage I or II, or NYHA functional class I or II) now constitute approximately 85% to 90% of patients with newly diagnosed ATTR-CM at specialized amyloid centers across many regions of the world.[8,10] These patients may derive a greater benefit from acoramidis treatment than those with more advanced ATTR-CM. This is consistent with a proposed mechanism of action of acoramidis being the reduction in the formation and deposition of newly formed toxic amyloid fibrils. Furthermore, although the reported efficacy analyses of acoramidis were conducted in the mITT cohort with eGFR ≥30 mL/min/1.73 m^2, a 25% lower rate of ACM was observed with acoramidis treatment compared with placebo in the small subgroup of participants (n = 21) with severe renal impairment (eGFR <30 mL/min/1.73 m^2).

To contextualize the clinical efficacy observed with acoramidis, it is helpful to consider the study results obtained with sacubitril/valsartan and SGLT2 inhibitors, 2 recently approved heart failure treatments with Class I recommendations in the current heart failure diagnosis and treatment guidelines.[20,21] In trials, sacubitril/valsartan and SGLT2 inhibitors reduced the relative risk of cardiovascular death or CVH, compared with an active control or placebo, by 20% (median duration: 27 months) and 25% (median duration: 17 months), respectively, in patients with heart failure with reduced ejection fraction, and by 13% (median duration: 35 months) and 20% (median duration: 27 months) in those with heart failure with

FIGURE 2 Kaplan-Meier Curve for the Time to First CVH Through Month 30



Data are shown for the modified intention-to-treat population. Cardiovascular-related hospitalizations (CVHs) are those that were adjudicated as cardiovascular related and nonelective by a Clinical Events Committee, including events of clinical interest. The time to first CVH was analyzed by using a Cox proportional hazards model that included treatment as an explanatory factor and baseline 6-minute walk distance as a covariate, stratified by randomization factors of genotype, N-terminal pro-B-type natriuretic peptide, and estimated glomerular filtration rate.

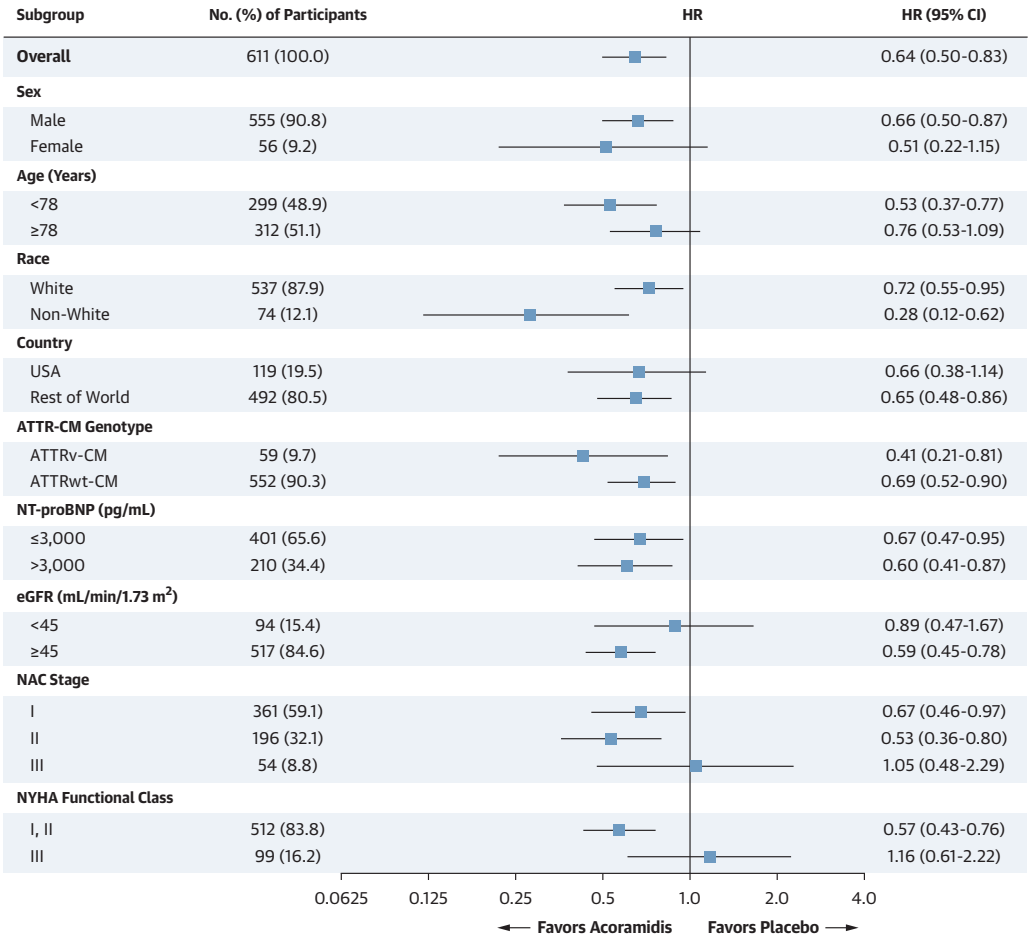
preserved ejection fraction (HFpEF).[22-25] Although sacubitril/valsartan and SGLT2 inhibitor trials involved participants with different types of heart failure, all studies conducted in ATTR-CM, heart failure with reduced ejection fraction, and HFpEF included optimal standard-of-care background therapies at the time of study conduct. Acoramidis, however, is distinct, as it directly addresses the root cause of ATTR-CM, highlighting the potential of a targeted therapy.

Because patients with ATTR-CM aged >60 years may constitute up to 16% of cases of HFpEF,[26-28] and with CVH being the largest cause of hospital readmissions in the U.S. Medicare population (age ≥65 years),[29] further research is needed to determine the potential wider positive impact of acoramidis to decrease health care resource utilization and reduce the burden on health care systems.

STUDY STRENGTHS AND LIMITATIONS. One strength of the ATTRibute-CM study is that the efficacy of acoramidis was shown in a contemporary cohort of participants with ATTR-CM who were diagnosed at earlier disease stages and were optimally treated for their heart failure condition. The marked reduction in CVH is of particular clinical relevance in the current era, with patients newly diagnosed with ATTR-CM now living longer.[12]

Concomitant tafamidis was introduced in a subset of participants at variable times during the study (17.5% of participants overall, with an imbalance toward greater use in the placebo group compared with

FIGURE 3 Forest Plot for Subgroup Analysis of the Time to ACM or First CVH



Data are shown for the modified intention-to-treat population. ACM includes all-cause death, heart transplantation, and cardiac mechanical assist device implantation. CVHs are those that were adjudicated as cardiovascular related and nonelective by a Clinical Events Committee, including events of clinical interest. ATTR-CM = transthyretin amyloid cardiomyopathy; ATTRv-CM = variant transthyretin amyloid cardiomyopathy; ATTRwt-CM = wild-type transthyretin amyloid cardiomyopathy; eGFR= estimated glomerular filtration rate; NAC = National Amyloidosis Centre; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Figure 1.

acoramidis). This imbalance between groups may have led to an underestimation of the effects of acoramidis. Although we have reported here the results of adjusting for tafamidis using a time-varying covariate, we have not used tafamidis as a standalone baseline subgroup. The subgroup approach was not implemented because it would have introduced guarantee-time bias (because tafamidis initiation as a concomitant treatment could not occur unless a participant had survived for 12 months).[30] In addition, a small proportion of participants (2.1% overall) received SGLT2 inhibitors at baseline. Recent observational retrospective studies have shown that SGLT2 inhibitors may confer a benefit in ATTR-CM.[31,32] Finally, ATTRibute-CM included a relatively low proportion of women, of participants who identified as Black or African American, and of participants with ATTRv-CM. Recent studies have reported underdiagnosis of ATTR-CM in women and in Black or African-American individuals, as well as

continuing challenges in enrolling underrepresented populations in clinical trials.[33-37] ATTRv-CM is known to have a worse prognosis than ATTRwt-CM.[4]

CONCLUSIONS

Acoramidis treatment led to reductions in ACM or CVH, and in CVH alone, that were large in magnitude and were apparent early, starting at month 3. The efficacy of acoramidis was observed across multiple endpoints and subgroups. The internal consistency of the ATTRibute-CM study results shows the robustness of the efficacy of acoramidis treatment to improve clinical outcomes in a contemporary ATTR-CM patient population. Further studies, including the currently ongoing open-label extension of ATTRibute-CM (NCT04988386), will provide further insights into the long-term efficacy and safety of acoramidis.

ACKNOWLEDGMENTS The authors thank the participating patients, their families, and the caregivers, investigators, and study center staff for their participation. The authors thank Jing Du, MD, MS, and Kevin Wang, PhD, from BridgeBio Pharma, Inc, for help with additional statistical analyses. Under the guidance from the authors, Isabella Inzani, PhD, and Michael Dyle, PhD, of Oxford PharmaGenesis provided medical writing assistance, which was funded by BridgeBio Pharma, Inc. Editorial support was provided by Shweta Rane, PhD, CMPP, of BridgeBio Pharma, Inc. The interpretation of the data and the decision to submit the manuscript to the journal were done independently by the authors without any influence from the sponsor of the study.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The ATTRibute-CM study was funded by BridgeBio Pharma, Inc. Dr Judge has received consultancy fees from Alexion Pharmaceuticals, Alleviant Medical, Alnylam Pharmaceuticals, Attralus, Cytokinetics, Lexeo Therapeutics, Novo Nordisk, Pfizer, Renovacor, and Tenaya Therapeutics; and his institution has received clinical trial funding from Array Biopharma, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), MyoKardia, and Pfizer. Dr Alexander has served as a consultant, advisor, or speaker for Arbor Biotechnologies, Attralus, Intellia Therapeutics, and Prothena. Dr Cappelli has served as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, Amicus Therapeutics, AstraZeneca, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Novo Nordisk, and Pfizer. Dr Fontana has served as a consultant, advisor, or speaker for Akcea Therapeutics, Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Global Services, Novo Nordisk, and Pfizer; and has received research grants from BridgeBio Pharma, Inc (formerly Eidos Therapeutics) and Pfizer. Dr Garcia-Pavia has served as a consultant, advisor, or speaker for Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio (formerly Eidos Therapeutics), Intellia Therapeutics, Ionis Pharmaceuticals, Neuroimmune, Novo Nordisk, and Pfizer; and his institution has received research and/or educational funding from Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Intellia Therapeutics, Novo Nordisk, and Pfizer. Dr Gibbs is an employee of BridgeBio Pharma, Inc; and has served as a speaker, advisory board member, or steering committee member for AbbVie, Alnylam Pharmaceuticals, Bristol Myers Squibb, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Pfizer, and Takeda. Dr Grogan has served as a researcher for Alnylam Pharmaceuticals, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Intellia Therapeutics, Novo Nordisk, Janssen Pharmaceuticals, and Pfizer; and has served as a consultant, advisor, or speaker for Alnylam, BridgeBio, Pfizer, Janssen Pharmaceuticals, and Novo Nordisk. Dr Hanna has served as a consultant, advisor, or speaker for Alexion Pharmaceuticals, Alnylam Pharmaceuticals, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Ionis Pharmaceuticals, and Pfizer. Dr Masri has served as a researcher for Attralus, Cytokinetics, Ionis Pharmaceuticals, and Pfizer; and has served as a consultant, advisor, or speaker for Akros Pharma, Alexion Pharmaceuticals, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BioMarin Pharmaceutical, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Bristol Myers Squibb, Cytokinetics, Haya Therapeutics, Ionis Pharmaceuticals, Lexicon Pharmaceuticals, Pfizer, Prothena Biosciences, and Tenaya Therapeutics. Dr Maurer has served as a researcher for the National Institutes of Health (R01HL139671 and R01AG081582-01), Alnylam Pharmaceuticals, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Ionis Pharmaceuticals, Pfizer, Attralus, and Intellia Therapeutics; and has served as a consultant or advisor for Akcea Therapeutics, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Intellia Therapeutics, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer. Dr Obici has served as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, AstraZeneca, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), Ionis Pharmaceuticals, Novo Nordisk, Pfizer, and Sobi-Swedish Orphan Biovitrum. Dr Soman has served as a researcher for Pfizer; and has served as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, BridgeBio Pharma, Inc (formerly Eidos Therapeutics), and Pfizer. Drs Cao, Lystig, Tamby, Siddhanti, Castaño, Katz, and Fox are employees and stockholders of BridgeBio Pharma, Inc. Dr Mahaffey has received research support from the American Heart Association, Apple, Inc, Bayer, California Institute Regenerative Medicine, CSL Behring, Eidos, Ferring, Gilead, Google, Idorsia, Johnson and Johnson, Luitpold, Novartis, PAC-12, Precordior, and Sanifit; has served as a consultant for Applied Therapeutics, Bayer, Bristol Myers Squibb, BridgeBio, CSL Behring, Elsevier, Fosun Pharma, Human, Johnson and Johnson, Moderna, Myokardia, Novartis, Novo Nordisk, Otsuka, Phasebio, Portola, Quidel, and Theravance; and has equity in Human, Medeloop, Precordior, and Regencor. Dr Gillmore has served as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio Pharma, Inc, Intellia Therapeutics, Ionis Pharmaceuticals, Lycia, and Pfizer.

ADDRESS FOR CORRESPONDENCE: Dr Daniel P. Judge, Division of Cardiology, Medical University of South Carolina, 30 Courtenay Drive, Room 326, Gazes, MSC 592, Charleston, South Carolina 29425, USA. E-mail: Judged@musc.edu.

REFERENCES

1. Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. *Nat Rev Cardiol*. 2010;7(7):398–408.

2. Ruberg FL, Maurer MS. Cardiac amyloidosis due to transthyretin protein: a review. *JAMA*. 2024;331(9):778–791.

3. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation*. 2019;140(1):16–26.

4. Nativi-Nicolau J, Judge DP, Hoffman JE, et al. Natural history and progression of transthyretin amyloid cardiomyopathy: insights from ATTR-ACT. *ESC Heart Fail*. 2021;8(5):3875–3884.

5. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81(11):1076–1126.

6. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2021;42(16):1554–1568.

7. Brito D, Albrecht FC, de Arenaza DP, et al. World Heart Federation consensus on transthyretin amyloidosis cardiomyopathy (ATTR-CM). *Glob Heart*. 2023;18(1):59.

8. Ioannou A, Patel RK, Razvi Y, et al. Impact of earlier diagnosis in cardiac ATTR amyloidosis over the course of 20 years. *Circulation*. 2022;146(22):1657–1670.

9. Achten A, van Empel VPM, Weerts J, et al. Changes in the diagnostic trajectory of transthyretin cardiac amyloidosis over six years. *Heart Vessels*. 2024;39(10):857–866.

10. Nativi-Nicolau J, Siu A, Dispenzieri A, et al. Temporal trends of wild-type transthyretin amyloid cardiomyopathy in the transthyretin amyloidosis outcomes survey. *JACC CardioOncol*. 2021;3(4):537–546.

11. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2024;390(2):132–142.

12. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2025;392:33–44.

13. Penchala SC, Connelly S, Wang Y, et al. AG10 inhibits amyloidogenesis and cellular toxicity of the familial amyloid cardiomyopathy-associated V122I transthyretin. *Proc Natl Acad Sci U S A*. 2013;110(24):9992–9997.

14. Judge DP, Heitner SB, Falk RH, et al. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2019;74(3):285–295.

15. Miller M, Pal A, Albusairi W, et al. Enthalpy-driven stabilization of transthyretin by AG10 mimics a naturally occurring genetic variant that protects from transthyretin amyloidosis. *J Med Chem*. 2018;61(17):7862–7876.

16. Ji A, Wong P, Judge DP, Graef IA, Fox J, Sinha U. Acoramidis produces near-complete TTR stabilization in blood samples from patients with variant transthyretin amyloidosis that is greater than that achieved with tafamidis. *Eur Heart J*. 2023;44(suppl 2):ehad655.989.

17. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J*. 2018;39(30):2799–2806.

18. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med*. 1999;18(11):1341–1354.

19. Nichols GA, Pesa J, Sapp DS, Patel A. The association between heart failure hospitalization and self-reported domains of health. *Qual Life Res*. 2020;29(4):953–958.

20. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *JACC*. 2022;79(17):e263–e421.

21. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726.

22. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993–1004.

23. Usman MS, Siddiqi TJ, Anker SD, et al. Effect of SGLT2 inhibitors on cardiovascular outcomes across various patient populations. *J Am Coll Cardiol*. 2023;81(25):2377–2387.

24. Jaiswal A, Jaiswal V, Ang SP, et al. SGLT2 inhibitors among patients with heart failure with preserved ejection fraction: a meta-analysis of randomised controlled trials. *Medicine (Baltimore)*. 2023;102(39):e34693.

25. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381(17):1609–1620.

26. Aimo A, Merlo M, Porcari A, et al. Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. *Eur J Heart Fail*. 2022;24(12):2342–2351.

27. Merlo M, Pagura L, Porcari A, et al. Unmasking the prevalence of amyloid cardiomyopathy in the real world: results from Phase 2 of the AC-TIVE study, an Italian nationwide survey. *Eur J Heart Fail*. 2022;24(8):1377–1386.

28. Garcia-Pavia P, Garcia-Pinilla JM, Lozano-Bahamonde A, et al. Prevalence of transthyretin cardiac amyloidosis in patients with heart failure with preserved ejection fraction: the PRACTICA study. *Rev Esp Cardiol (Engl Ed)*. Published online July 31, 2024. https://doi.org/10.1016/j.rec.2024.07.005

29. Jiang HJ, Barrett ML. *Clinical conditions with frequent, costly hospital readmissions by payer, 2020. HCUP Statistical Brief #307*. Rockville, MD: Agency for Healthcare Research and Quality; April 2024. https://hcup-us.ahrq.gov/reports/statbriefs/SB307-508.pdf

30. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. *J Clin Oncol*. 2013;31(23):2963–2969.

31. Porcari A, Cappelli F, Nitsche C, et al. SGLT2 inhibitor therapy in patients with transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2024;83(24):2411–2422.

32. Sivamurugan A, Byer SH, Grewal US, Dominic P. Impact of SGLT2 inhibitors on the outcomes of patients with cardiac arrythmias and transthyretin cardiac amyloidosis. *Heart Rhythm*. Published online September 6, 2024. https://doi.org/10.1016/j.hrthm.2024.09.002

33. Bruno M, Castano A, Burton A, Grodin JL. Transthyretin amyloid cardiomyopathy in women: frequency, characteristics, and diagnostic challenges. *Heart Fail Rev*. 2021;26(1):35–45.

34. Patel RK, Ioannou A, Razvi Y, et al. Sex differences among patients with transthyretin amyloid cardiomyopathy—from diagnosis to prognosis. *Eur J Heart Fail*. 2022;24(12):2355–2363.

35. Alexander KM, Orav J, Singh A, et al. Geographic disparities in reported US amyloidosis mortality from 1979 to 2015: potential underdetection of cardiac amyloidosis. *JAMA Cardiol*. 2018;3(9):865–870.

36. Michos ED, Reddy TK, Gulati M, et al. Improving the enrollment of women and racially/ethnically diverse populations in cardiovascular clinical trials: an ASPC practice statement. *Am J Prev Cardiol*. 2021;8:100250.

37. DeFilippis EM, Echols M, Adamson PB, et al. Improving enrollment of underrepresented racial and ethnic populations in heart failure trials: a call to action from the Heart Failure Collaboratory. *JAMA Cardiol*. 2022;7(5):540–548.

KEY WORDS acoramidis, all-cause mortality, ATTR-CM, cardiovascular-related hospitalization, transthyretin

APPENDIX For the Statistical Analysis Plan, Study Protocol, and supplemental tables, please see the online version of this paper.