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ORIGINAL ARTICLE

Effects of Acoramidis on Kidney Function in Transthyretin Amyloid Cardiomyopathy

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BACKGROUND: Acoramidis achieves near-complete (≥90%) transthyretin stabilization and is approved to reduce cardiovascular-related hospitalization in transthyretin amyloid cardiomyopathy. Its effects on kidney function are not well characterized.

METHODS: Data from randomized phase 2 (N=49) and phase 3 (N=632) studies in transthyretin amyloid cardiomyopathy were included. The estimated glomerular filtration rate (eGFR) slope was generated using a linear spline mixed-effects model. The urinary albumin-to-creatinine ratio was measured longitudinally. Relationships between changes in kidney function and clinical outcomes were explored using Cox proportional hazards models.

RESULTS: Acoramidis initiation resulted in a modest acute dip in eGFR that was dose-dependent, reversible, and not associated with adverse kidney-related events. At Day 28, the mean (±SE) dip in eGFR from baseline with acoramidis was 8.5±0.48 mL/min per 1.73 m^2; the placebo-corrected reduction in the urinary albumin-to-creatinine ratio was 15.5% (95% CI, 0.4%–28.4%; P=0.044). The rate of decline in kidney function (chronic eGFR slope) was significantly improved with acoramidis versus placebo (−1.01 versus −3.48 mL/min per 1.73 m^2 per year; P<0.001), and the reduction in the urinary albumin-to-creatinine ratio was sustained (13.7% [95% CI, 1.7%–24.2%]; P=0.026) over time. Concomitant tafamidis use did not influence the chronic eGFR slope in either arm. Comparing acoramidis versus placebo subgroups with acute eGFR dips ≥ the median (4.89 mL/min per 1.73 m^2) favored acoramidis for all-cause mortality or cardiovascular-related hospitalization (hazard ratio, 0.42 [95% CI, 0.22–0.78]; P=0.006; P interaction=0.043) and cardiovascular-related hospitalization (hazard ratio, 0.34 [95% CI, 0.17–0.66]; P=0.002, P interaction=0.025). Within the placebo arm, eGFR dips portended worse outcomes.

CONCLUSIONS: Acoramidis initiation resulted in an acute dip in eGFR and reductions in both the chronic eGFR slope and urinary albumin-to-creatinine ratio versus placebo without adverse kidney-related events. Acoramidis effects on kidney function may be mediated through direct kidney-protective hemodynamic effects. Importantly, the acute dip in eGFR was associated with a reduced risk of adverse clinical outcomes within the first year.

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Key Words: arm ■ creatinine ■ hemodynamics ■ kidney ■ tafamidis

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive disease characterized by destabilization of native, tetrameric transthyretin (TTR).[1–3] Dissociation of TTR into its constituent monomers causes them to misfold and aggregate as circulating, toxic amyloidogenic oligomers that accumulate as insoluble amyloid fibrils in a range of tissues and organs, particularly the heart.[1–3] The resultant infiltrative

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WHAT IS NEW?

- This study suggests potential kidney-protective effects of acoramidis based on an improved chronic estimated glomerular filtration rate slope.
- The magnitude of the acute estimated glomerular filtration rate dip in participants treated with acoramidis was positively associated with a reduction in early cardiovascular outcomes.
- The estimated glomerular filtration rate dip was accompanied by an early and sustained reduction in the urinary albumin-to-creatinine ratio, qualitatively similar to the effects of kidney-protective drugs such as angiotensin-converting enzyme inhibitors and sodium-glucose cotransporter-2 inhibitors.
- An acute estimated glomerular filtration rate dip and a reduced urinary albumin-to-creatinine ratio have not been reported for other transthyretin amyloid cardiomyopathy therapies and may be independent of acoramidis' anti-amyloidogenic pharmacology.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The effects of acoramidis on kidney function resemble the pattern observed with kidney-protective drugs that act directly on the kidney.
- As with angiotensin-converting enzyme inhibitors, the initial bump in creatinine should not trigger acoramidis discontinuation; the dip is a sign of a kidney-protective effect and is associated with improved long-term outcomes.
- Disease-modifying treatments for transthyretin amyloid cardiomyopathy have markedly improved survival; as a result, the effects of such treatments on preserving kidney function, an independent predictor of survival in this disease, are becoming increasingly important.

Nonstandard Abbreviations and Acronyms

ACM	all-cause mortality
ATTR-CM	transthyretin amyloid cardiomyopathy
CVH	cardiovascular-related hospitalization
eGFR	estimated glomerular filtration rate
HR	hazard ratio
IQR	interquartile range
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OLE	open-label extension
TTR	transthyretin
UACR	urinary albumin-to-creatinine ratio

cardiomyopathy leads to progressive and often fatal heart failure.[4]

Acoramidis, a selective oral TTR stabilizer, promptly achieves near-complete (≥90%) TTR stabilization upon initiation of treatment.[5–10] Acoramidis is approved for the treatment of wild-type or variant ATTR-CM in adults to reduce cardiovascular death and cardiovascular-related hospitalization (CVH)[6] and has been demonstrated to improve a broad spectrum of outcomes, such as reducing the risk of all-cause mortality (ACM) and CVH, as well as improving functional capacity and health-related quality of life.[10–12] Prespecified and post hoc analyses identified a reduction in CVH with acoramidis, with a early separation of the event curves.[10–12]

During the acoramidis clinical development program, the pattern of an early, modest dip in estimated glomerular filtration rate (eGFR) was observed upon initiation of therapy. The goal of the current analysis was to provide an in-depth description of the changes in kidney function associated with acoramidis treatment and their potential clinical implications. These include a possible relationship between the acute dip in eGFR and the reductions in death or CVH and CVH alone.

METHODS

Data Availability

Requests for access to study data (submitted to MedInfo@BridgeBio.com) will be evaluated by BridgeBio, and data will be made available to qualified academic investigators upon approval of a research or study proposal and execution of a data-sharing agreement.

Study Design and Participants

The phase 2, randomized, double-blind safety and efficacy study of acoramidis in participants with ATTR-CM (NCT03458130) has been previously reported.[5] Forty-nine individuals were randomized to receive either acoramidis hydrochloride 400 mg (n=16) or 800 mg (n=16), equivalent to acoramidis 356 mg or 712 mg, respectively, or matching placebo (n=17) twice daily for 28 days, followed by a 7- to 14-day washout and safety follow-up (Figure 1A). Forty-seven participants entered the open-label extension (OLE) study AG10-202 (NCT03536767; median follow-up 54 months), with 20 participants completing a full 72 months of therapy in the OLE.

The phase 3, randomized, double-blind, placebo-controlled ATTRibute-CM study (NCT03860935) and its OLE study (NCT04988386) have been previously described.[11,13] In ATTRibute-CM, 632 participants with ATTR-CM were randomized 2:1 to receive acoramidis hydrochloride 800 mg (n=421) or matching placebo (n=211) twice daily for 30 months (Figure 1B). After 12 months, there was a per-protocol option for the concomitant use of tafamidis (drop-in) at the discretion of the treating physician.

Participants who completed treatment through Month 30 and who met the eligibility criteria were invited to enroll in the ongoing OLE study of acoramidis 800 mg daily, for which kidney function data up to Month 54 are available. Participants who had previously received tafamidis in ATTRibute-CM were required to discontinue it before enrolling in the OLE.

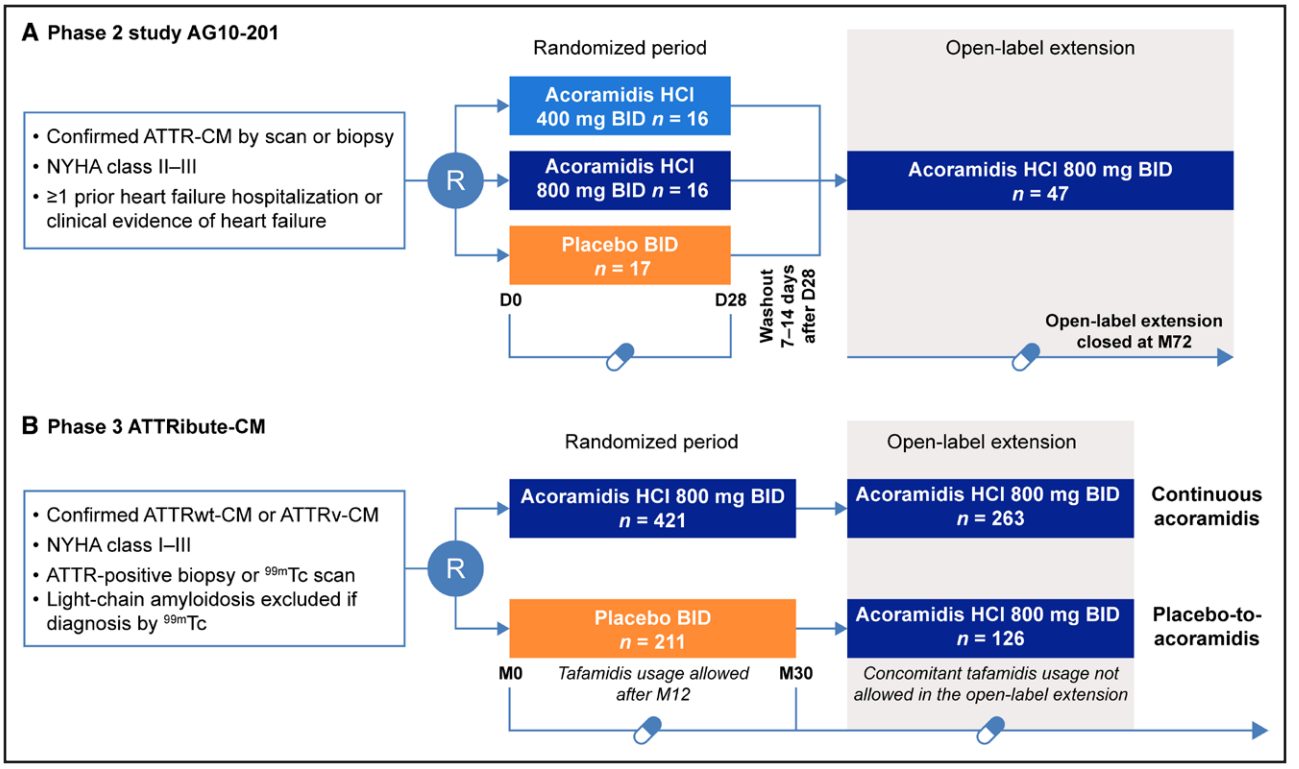

Figure 1. Study designs of the phase 2 study AG10-201 and the phase 3 ATTRibute-CM study.
A, In the phase 2 study AG10-201, participants were randomized in a 1:1:1 ratio to receive acoramidis hydrochloride (HCl) 400 mg (n=16), acoramidis HCl 800 mg (n=16), or placebo (n=17). After the Day 28 visit, participants entered a washout period of 7 to 14 days. Participants who completed AG10-201 were invited to enroll in the open-label extension, in which all enrolled participants received acoramidis HCl 800 mg (n=47). **B**, In the phase 3 ATTRibute-CM study, participants were randomized in a 2:1 ratio to receive acoramidis HCl 800 mg (n=421) or placebo (n=211). Numbers of participants reflect the intention-to-treat population which included participants with Stage 4 chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] between 15 and 30 mL/min per 1.73 m^2). Participants who completed 30 months of the ATTRibute-CM study and met the open-label extension (OLE) eligibility criteria were invited to enroll in the open-label extension. In the open-label extension, participants who received acoramidis in ATTRibute-CM continued to receive it (continuous acoramidis, n=263), and participants who received placebo in ATTRibute-CM switched to acoramidis (placebo-to-acoramidis, n=126). In the phase 2 study, eGFR was analyzed from blood samples taken at baseline and every 7 days (±3) in the randomized period, and once during the washout period. In the phase 3 study, eGFR was analyzed from blood samples taken at baseline, Day 28, and every 3 months (±7 days) in the randomized period, and at Months 1, 6, 12, 18, and 24 of the OLE. ^{99m}Tc indicates technetium-99 m; ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; BID, twice daily; D, day; M, month; and NYHA, New York Heart Association.

The phase 2 study AG10-201 and its OLE study AG10-202, and the phase 3 study ATTRibute-CM and its OLE study AG10-304, were approved by the institutional review board or ethics committee at each participating study site. All participants provided written informed consent.

Assessments

In addition to clinical efficacy measures, pharmacokinetic and pharmacodynamic assessments, adverse events, and safety laboratory tests, including serum creatinine (by an enzymatic method), were measured at each study visit. In the phase 2 study, serum creatinine was measured in a central laboratory using the Beckman Coulter 5800 analyzer (Beckman Coulter Diagnostics, Brea, CA). In the phase 3 study, serum creatinine assessments were performed in a central laboratory using the Abbott ARCHITECT system (Abbott, Farmington, NY, and Dublin, Ireland). The urinary albumin-to-creatinine ratio (UACR) was calculated from urinary creatinine and albumin measured using the Abbott ARCHITECT system.

Statistical Analyses

eGFR Slope Analyses

eGFR slopes were derived using a linear spline mixed-effects model based on eGFR values calculated from observed measurements of serum creatinine. The model included a change point ≈1 month after initiation of acoramidis, allowing the slope to vary before and after this change point. This structure was chosen to account for the acute dip in eGFR observed at the Day 28 visit following initiation of acoramidis. To evaluate the effect of acoramidis on the chronic eGFR trajectory, slopes estimated from the Day 28 visit to Month 30 (chronic eGFR slope) in ATTRibute-CM were compared between the acoramidis and placebo groups.

The model included time (in years) and the time-spline variable corresponding to the prespecified change point as fixed-effect covariates, with participant-level random intercepts and slopes for time and the time-spline variable.[14] Point estimates and associated 95% CIs for the slopes and slope differences were calculated using standardized formulae. As

sensitivity analyses, we applied a shared-parameter joint modeling approach linking longitudinal eGFR trajectories and time to ACM via participant-level random effects under nonignorable dropout assumptions.[14]

Analyses of Concomitant Tafamidis Use

As tafamidis drop-in could have influenced the analyses beyond Month 12 of the phase 3 study, ATTRibute-CM, we conducted sensitivity analyses of eGFR changes in the subgroups with and without tafamidis drop-in. These analyses were conducted both within the randomized period up to Month 30 and following entry into the OLE, in which all participants were treated with acoramidis (ie, all participants in the placebo arm received acoramidis only in the OLE, regardless of whether they had received concomitant tafamidis). Although drop-in was more frequent in the placebo arm, tafamidis drop-in occurred at random with respect to time on study but was sustained through Month 30 in those who completed the study and entered the OLE. Therefore, the change in kidney function in this subgroup of the placebo arm was also analyzed. The last visit before tafamidis drop-in for each participant was compared with the next visit following drop-in and with the acoramidis-alone (ie, without tafamidis drop-in) subgroup.

Acute Dip in eGFR and Clinical Outcomes

Landmark analyses were performed to assess the impact of the acute dip in eGFR on early cardiovascular-related clinical outcomes. In the landmark analyses, the potential association between the change from baseline in eGFR at the landmark time of Day 28 and the end points of the time to ACM or first CVH and first CVH alone over 12 months from the landmark time (ie, through 13 months from the time of randomization) was evaluated using Cox regression models. A treatment duration of 12 months was selected to try to isolate potential early, direct, kidney-mediated hemodynamic effects of acoramidis (resembling those of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or sodium-glucose cotransporter-2 inhibitors) from its later chronic myocardial disease-modifying effects and to avoid the potential influence of tafamidis drop-in.

Subgroup Analyses of Clinical Outcomes Based on eGFR Dip at Day 28

Subgroups were defined by participants with a dip in eGFR from baseline through Day 28 that was ≥ or < the median change from baseline in eGFR at Day 28. Cox proportional hazards models were used to estimate hazard ratios (HRs) for ACM or first CVH, and first CVH alone, for the overall study population and for subgroups with an eGFR dip greater than and less than the median between and within treatment arms. The overall Cox proportional hazards model was stratified by TTR genotype and baseline NT-proBNP (N-terminal pro-B-type natriuretic peptide) level at randomization and included treatment and baseline eGFR as covariates. For subgroup analyses, the eGFR dip subgroup and its interaction with treatment were additionally included.

The change from baseline in UACR was analyzed using a mixed-effects model for repeated measures. The dependent variable was the $\log_{10}$-transformed change from baseline in UACR. The model included treatment group as a fixed effect, visit (and its interaction with treatment group when assessing consistency over time), adjusted for baseline $\log_{10}$-transformed UACR, TTR genotype, log-transformed baseline NT-proBNP, and baseline eGFR. An unstructured covariance structure was used to account for within-participant correlations.

For the analysis of eGFR change from baseline in the phase 2 study, a mixed-effects model for repeated measures was used, with treatment group, visit, and treatment group-by-visit interaction as fixed effects, and the baseline eGFR value as a covariate.

RESULTS

Baseline Demographics and Clinical Characteristics in the Phase 2 and 3 Studies

The phase 2 study included 49 participants with ATTR-CM.[5] Baseline demographics and clinical characteristics are displayed in the Table. Participants overall had a mean (±SD) age of 74.1±6.6 years, and 14 (29%) participants had variant ATTR-CM. Overall, participants had relatively high baseline NT-proBNP concentrations (median, 2488 pg/mL [interquartile range (IQR), 1342–4058 pg/mL]). Of the 49 participants in the overall group, 46 (94%) were receiving diuretics at study entry. At baseline, the mean (±SD) serum creatinine was 1.31±0.32 mg/dL, and the mean (±SD) eGFR was 59.7±16.9 mL/min per 1.73 m^2.

The phase 3 ATTRibute-CM trial intention-to-treat population included 632 participants: acoramidis, n=421; placebo, n=211.[10] Baseline demographics and clinical characteristics are also presented in the Table. Overall, participants had a mean (±SD) age of 77.3±6.6 years, and 90.2% had wild-type disease. Participants in the overall group had relatively high baseline NT-proBNP concentrations (median, 2326 pg/mL [IQR, 1278–3910 pg/mL]), and 95% of participants were receiving diuretic therapy at the time of randomization. The mean (±SD) serum creatinine at baseline was 1.24±0.41 mg/dL, the mean (±SD) eGFR was 63.3±18.3 mL/min per 1.73 m^2, and the median (IQR) UACR was 30.32 (12.82–96.62) mg/g. Baseline medications in ATTRibute-CM have been previously described and were well balanced between the acoramidis and placebo groups.[11]

Results From the Phase 2 Randomized Study and the OLE

At Day 28, there was an acute dose-dependent dip in eGFR in the acoramidis 400 mg twice-daily and 800 mg twice-daily groups. The placebo-corrected dips in eGFR (change from baseline, mean±SE) were 5.44±2.31 mL/min per 1.73 m^2 (P=0.023) and 9.76±2.27 mL/min per 1.73 m^2 (P<0.001), respectively (Figure 2); the P value for the between-dose difference was 0.067. This dose-dependent dip in eGFR was fully reversible upon discontinuation of acoramidis during the washout period, returning to baseline values

Table. Phase 2 (AG10-201) and Phase 3 (ATTRibute-CM) Study Baseline Characteristics

	Phase 2 (AG10-201)				Phase 3 (ATTRibute-CM)		
	Acoramidis 400 mg (n=16)	Acoramidis 800 mg (n=16)	Placebo (n=17)	Overall (N=49)	Acoramidis 800 mg (n=421)	Placebo (n=211)	Overall (N=632)
Mean age, y (SD)	73.8 (5.7)	75.4 (6.8)	73.2 (7.4)	74.1 (6.6)	77.4 (6.5)	77.1 (6.8)	77.3 (6.6)
Male, n (%)	14 (87.5)	14 (87.5)	17 (100)	45 (91.8)	384 (91.2)	186 (88.2)	570 (90.2)
ATTRv-CM, n (%)	6 (37.5)	5 (31.3)	3 (17.6)	14 (28.6)	41 (9.7)	20 (9.5)	61 (9.7)
Median NT-proBNP, pg/mL (IQR)	3109 (1192, 6010)	2349 (1733, 3749)	2629 (1342, 3858)	2488 (1342, 4058)	2326 (1332, 4019)	2306 1128, 3754)	2326 (1278, 3910)
Mean Serum creatinine, mg/dL (SD)	1.38 (0.30)	1.31 (0.41)	1.25 (0.25)	1.31 (0.32)	1.24 (0.43)	1.23 (0.36)	1.24 (0.41)
Mean eGFR, mL/min per 1.73 m^2 (SD)	54.9 (15.6)	59.8 (17.4)	64.2 (17.2)	59.7 (16.9)	63.4 (18.2)	63.2 (18.4)	63.3 (18.3)
Median UACR, mg/g (IQR)	NA	NA	NA	NA	31.38 (12.55, 90.61)	29.17 (13.17, 104.84)	30.32 (12.82, 96.62)
Prior SGLT2i use, n (%)	0	0	0	0	8 (1.9)	5 (2.4)	13 (2.1)
Diuretics use, n (%)	15 (93.8)	14 (87.5)	17 (100)	46 (93.9)	395 (93.8)	204 (96.7)	599 (94.8)

ATTRv-CM indicates variant transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NA, not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2i, sodium-glucose cotransporter-2 inhibitor; and UACR, urinary albumin-to-creatinine ratio.

after acoramidis washout (7–14 days after Day 28; *P*=0.813 and *P*=0.930 for the 400 mg and 800 mg dose arms, respectively, compared with baseline values; Figure 2). In the placebo group, the mean change in eGFR from baseline to the end of washout was 0.01±2.42 mL/min per 1.73 m^2.

Forty-seven of the 49 (96%) participants elected to participate in the OLE, in which all participants were treated with acoramidis hydrochloride 800 mg. Upon resumption of treatment following the washout period, the acute dip in eGFR was 7.1±1.03 (95% CI, 5.03–9.18) mL/min per 1.73 m^2 at the first postinitiation visit (Day 14) in the OLE. Notably, eGFR remained relatively stable with acoramidis through the 72-month observation period when compared with the first visit following initiation of treatment in the OLE, with an eGFR slope of −1.67±0.52 mL/min per 1.73 m^2 per year (95% CI, −2.73 to −0.62).

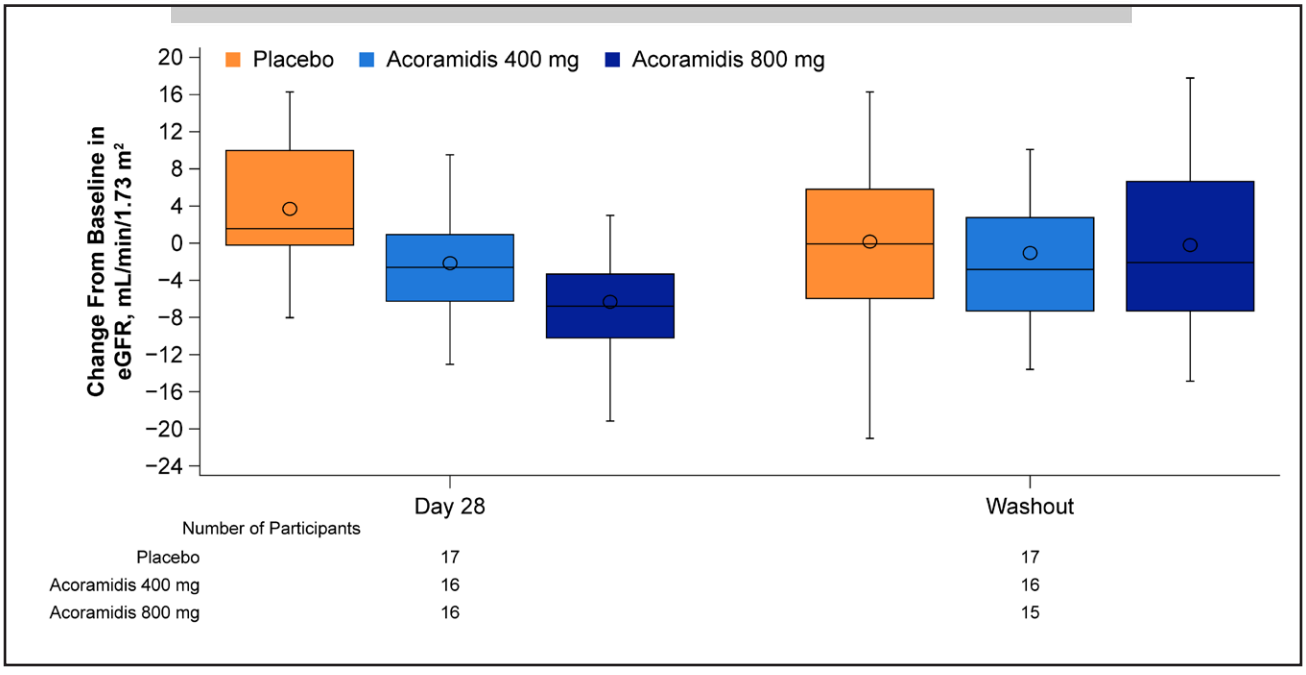

Figure 2. Change from baseline in estimated glomerular filtration rate (eGFR) in the phase 2 study AG10-201 at Day 28 and after acoramidis washout.
In AG10-201, the washout visit was 7 to 14 days after the Day 28 visit (or after the last dose for those participants who withdrew from the study before completion). Baseline for both the eGFR change at Day 28 and following washout was defined as the pretreatment eGFR in AG10-201. Circles in the boxes represent mean values and lines represent median values.

Observations From the Phase 3 ATTRibute-CM Study and Its OLE

Upon initiation of acoramidis therapy, an acute dip in eGFR of 8.5±0.48 (95% CI, 7.57–9.44) mL/min per 1.73 m^2 was observed (Day 28; Figure 3). No dip in eGFR was observed in the placebo group. There was no heterogeneity in the effect of acoramidis on the acute dip in eGFR across participants with chronic kidney disease stages ranging from stage 1 to 4 (interaction P=0.159).

Analysis of the eGFR slope revealed a chronic slope of −1.01 mL/min per 1.73 m^2 per year in the acoramidis arm versus −3.48 mL/min per 1.73 m^2 per year in the placebo arm from Day 28 through Month 30, yielding a placebo-corrected treatment effect for acoramidis of +2.47 mL/min per 1.73 m^2 per year (P<0.001). In addition, sensitivity analyses were performed to assess the potential impact of 3 nonignorable dropout mechanisms using a shared-parameter joint modeling approach.[14] Across all 3 models, the estimated treatment effect on chronic eGFR slope remained favorable for acoramidis versus placebo (+2.57, +2.63, and +2.69 mL/min per 1.73 m^2 per year; all P<0.001). Due to this stabilization, the 2 eGFR time-course curves nearly converged by Month 30, resulting in no statistically significant difference in eGFR between treatment groups at the end of the randomized treatment period (P=0.295). There was no heterogeneity in the effect of acoramidis on the improvement in the chronic eGFR slope across chronic kidney disease stages (interaction P=0.890).

Upon transition to acoramidis treatment at the initiation of the OLE, the placebo-to-acoramidis group demonstrated an acute dip in eGFR (mean±SE) at the Month 1 visit of 7.85±0.79 mL/min per 1.73 m^2, which recapitulated the changes observed in the acoramidis arm at Day 28 of the randomized study. Following this acute dip, the

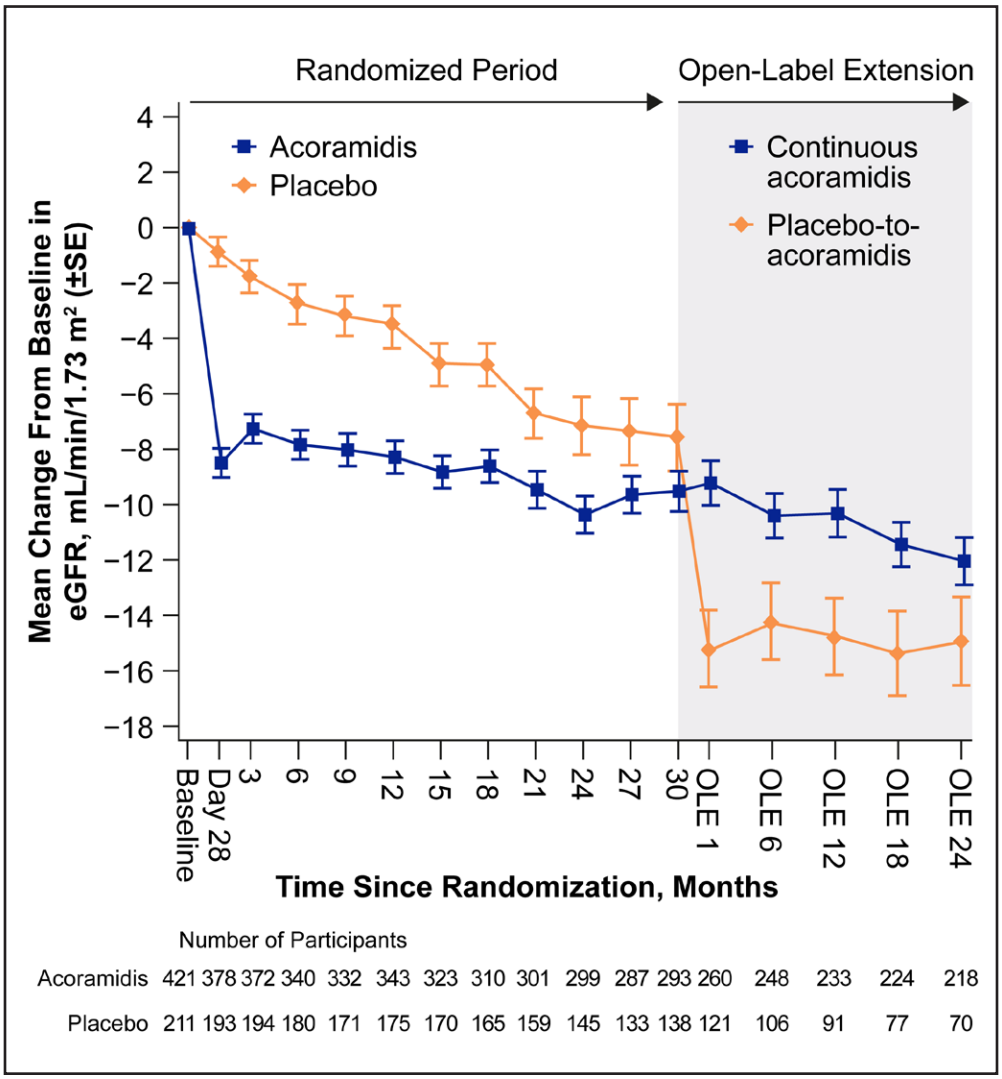

Figure 3. Change from baseline in estimated glomerular filtration rate (eGFR) in the Phase 3 ATTRibute-CM study and its open-label extension (OLE) study.
Data are for the intention-to-treat population. Participants who completed 30 months of the ATTRibute-CM study and met the eligibility criteria were invited to enroll in the OLE study. Data are presented as mean (±SE).

eGFR was stable, with a chronic eGFR slope of −0.05 (95% CI, −1.28 to 1.19) mL/min per 1.73 m^2 per year.

Potential Influence of Tafamidis Drop-in

Per protocol, concomitant (drop-in) tafamidis use was permitted at the investigator's discretion after 12 months in the randomized period of the phase 3 study. A total of 107 participants received drop-in tafamidis: 61 participants in the acoramidis arm and 46 participants in the placebo arm (P=0.021).

There was no acute dip in eGFR upon tafamidis initiation in participants receiving placebo following tafamidis drop-in (Figure 4A). Furthermore, there was no additional acute dip in eGFR in those already receiving acoramidis who initiated tafamidis. Between Month 12 (when tafamidis drop-in was permitted) and Month 30 (the end of the double-blind randomized treatment period), there were no significant differences in eGFR slope with tafamidis drop-in, including in the (1) overall population (regardless of randomized treatment; P=0.402), (2) placebo arm (P=0.581), and (3) acoramidis arm (P=0.515).

In participants in the placebo group who transitioned to acoramidis in the OLE study, there was no difference in the eGFR dip at Month 1 of the OLE study between those receiving tafamidis versus those not receiving tafamidis: the acute dip in eGFR was 7.74±1.97 mL/min per 1.73 m^2 versus 7.87±0.87 mL/min per 1.73 m^2, respectively (P=0.948; Figure 4B). These dips recapitulated the acute dip in eGFR observed in the acoramidis arm following randomization.

Analysis of Change From Baseline in Albuminuria

UACR was measured longitudinally in spot urine samples collected at study visits. Baseline median UACR was 31.38 (IQR, 12.55–90.61) mg/g in the acoramidis arm and 29.17 (IQR, 13.17–104.84) mg/g in the placebo arm. Over the 30-month follow-up period of the trial, there was a placebo-corrected 13.7% (95% CI, 1.7%–24.2%; P=0.026) reduction in albuminuria in the acoramidis arm versus the placebo arm. This change occurred as early as Day 28, with a 23.6% (95% CI, 15.9%–30.6%) reduction in UACR with acoramidis versus 9.5% (95% CI, −3.4% to 20.8%) with placebo, corresponding to a placebo-corrected reduction of 15.5% (95% CI, 0.4%–28.4%; P=0.044). The improvement in UACR with acoramidis versus placebo was stable throughout follow-up, as indicated by a nonsignificant visit-by-treatment interaction (P=0.810).

Relationship Between the Acute eGFR Dip and Clinical Outcomes

To explore the early separation between the acoramidis and placebo time-to-first-event curves for ACM or

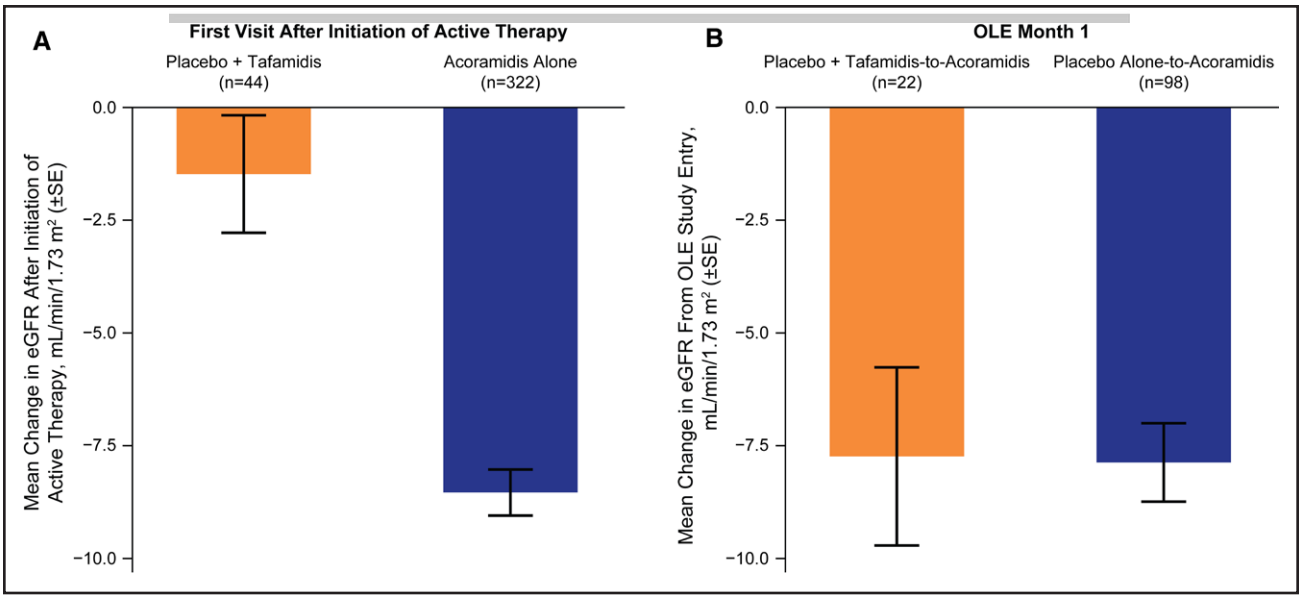

Figure 4. Change in estimated glomerular filtration rate (eGFR) in the phase 3 ATTRibute-CM study from before, and after, initiating active therapy in the randomized period, and after Month 1 in the open-label extension (OLE).
Data are for the intention-to-treat population. The placebo+tafamidis group represents data from participants in the placebo arm of ATTRibute-CM who received tafamidis at any time after 12 months in the study. **A**, Data represent the change in eGFR from before the start of treatment with acoramidis or tafamidis to the first visit following the start of treatment in the ATTRibute-CM parent study among participants who dropped in (ie, received tafamidis in the placebo group) at any time between Month 12 and Month 30 and among those in the acoramidis group. **B**, Data represent the change in eGFR from initiation of acoramidis in the ATTRibute-CM OLE study to Month 1 of the OLE (ie, 1 month after transition from placebo to acoramidis for participants randomized to placebo in the randomized controlled trial).

CVH, and for CVH alone in ATTRibute-CM, and the acute dip in eGFR, a landmark analysis was conducted from Day 28 through 12 months following the landmark time (ie, through Month 13 from randomization) using Cox regression models. To explore the additive influence of the acute eGFR dip on the 12-month landmark analysis, the population distribution of the change from baseline in eGFR at Day 28 in each arm was initially characterized.

The overall population median dip from baseline in eGFR at Day 28 was 4.89 mL/min per 1.73 m^2. Subgroups with a dip above or below the median were then used to evaluate whether a greater eGFR dip enhanced or diminished the treatment effect of acoramidis.

Event-free survival curves for participants in the acoramidis group with an eGFR dip greater than the median visually separated at Month 3, favoring the subgroup with a larger eGFR dip (P=0.032 for ACM or first CVH and P=0.007 for first CVH; Figure 5). In the placebo arm, the opposite was observed: patients with a larger eGFR dip experienced worse outcomes.

As a reference, acoramidis treatment was associated with an overall hazard reduction in the time to first event (ACM or CVH) through 12 months from the landmark time of Day 28 (ACM or CVH HR, 0.67 [95% CI, 0.46–0.98]; P=0.037; CVH alone HR, 0.59 [95% CI, 0.40–0.89]; P=0.011; Figure 6), consistent with the overall results for these end points over the entire course of the study.[11] The comparison of the time to first event for ACM or CVH between the acoramidis and placebo subgroups with a larger eGFR dip favored acoramidis, with an HR of 0.42 (95% CI, 0.22–0.78; P=0.006; Figure 6A), whereas a neutral finding was noted for those with smaller eGFR dips (HR, 0.94 [95% CI, 0.58–1.53]; P=0.811). Similar results were obtained in analyses for CVH alone (acoramidis versus placebo for the subgroup with a larger eGFR dip: HR, 0.34 [95% CI, 0.17–0.66]; P=0.002; Figure 6B).

The subgroups within each treatment arm for both the composite end point of the time to first event for ACM or CVH and CVH alone were compared. A trend within the acoramidis treatment arm favoring a larger eGFR dip was observed. The effect modification by an acute dip in eGFR for both ACM or CVH and CVH alone was statistically significant (interaction P=0.043 for ACM or CVH; interaction P=0.025 for CVH alone). Opposite trends were observed in the placebo arm subgroups, favoring the smaller eGFR dips for both treatment arm comparisons (Figure 6).

Clinical Safety

The changes in eGFR described above were not associated with imbalances in kidney-related adverse events or with outcomes of death, drug discontinuation, or progression to end-stage kidney disease. Three participants had fatal, worsening kidney function events; all were in the placebo group (1.4%). The study drug was withdrawn due to worsening kidney function events in 2 (0.5%) participants in the acoramidis group and 2 (0.9%) participants in the placebo group. One participant in each treatment group was reported to progress to end-stage kidney disease (0.2% and 0.5% in the acoramidis and placebo treatment groups, respectively), despite the inclusion of individuals with advanced chronic kidney disease in the trial.

DISCUSSION

In the current study, several important findings related to the reproducible effects of acoramidis on kidney function are presented. First, acoramidis induced a significant, dose-dependent acute dip in eGFR within the first month of treatment that did not progress over time. The acute dip in eGFR was also fully reversible upon cessation of therapy and was not associated with adverse kidney-related clinical outcomes or treatment discontinuations. Second, the acute dip in eGFR was temporally accompanied by an acute, significant, and persistent improvement in UACR. When the chronic eGFR slope from Day 28 through Month 30 was compared between the acoramidis and placebo arms, active treatment led to a slower decline in kidney function in the acoramidis arm. Moreover, during long-term follow-up, a slower decline in the eGFR slope occurred with continued acoramidis treatment. These acute and chronic changes in kidney function were neither observed nor altered by tafamidis drop-in. Finally, the acute dip in eGFR at Day 28 with acoramidis initiation was positively associated with improved outcomes of ACM or first CVH, and CVH alone, within the subsequent 12 months of the trial. Conversely, greater reductions in eGFR from baseline to Day 28 in the placebo arm were associated with worse outcomes.

The rapidity with which these changes in kidney function were observed is similar to the previously reported observation of early separation of the event-free survival curves for ACM or CVH (with visual separation by 3 months),[11] and the cumulative cardiovascular-related mortality or recurrent CVH curves (demonstrating a numerical difference in events within 1 month).[12] These very early benefits from acoramidis treatment may be unlikely to arise from the primary therapeutic mechanism of reducing myocardial amyloid accumulation, which is thought to take months to years to produce clinically meaningful changes. Acute myocardial effects from arresting the accumulation of toxic amyloidogenic oligomeric precursors could be postulated as a driving factor, but early reductions in clinical outcomes have not consistently been reported in similar trials of ATTR-CM therapies. From the perspective of the kidney, an acute improvement in cardiac performance and heart failure severity might generally be expected to result in either

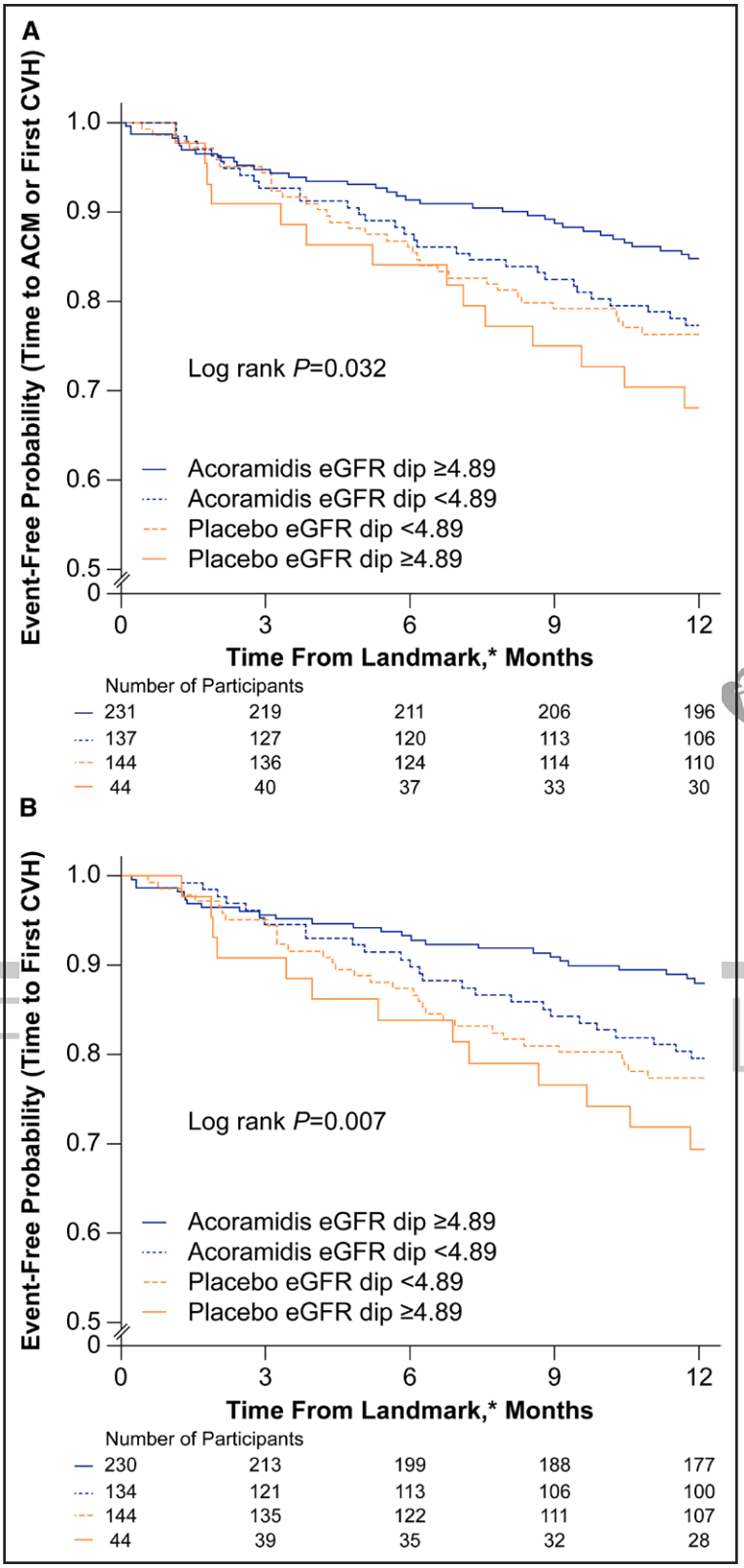

Figure 5. Time to first cardiovascular hospitalization and mortality outcomes by estimated glomerular filtration rate (eGFR) dip at Day 28.

Kaplan-Meier curves generated from a landmark analysis that was conducted with the landmark defined as the last study day of the Day 28 visit; participants event-free at the landmark time were followed for an additional 12 months for outcome assessment, according to the subgroups defined by an acute eGFR dip greater or less than the overall population median of 4.89 mL/min per 1.73 m^2 at Day 28. **A**, Time-to-first event for ACM or CVH. **B**, Time-to-first event for CVH alone. *12-month analysis initiated at Day 28 landmark. ACM indicates all-cause mortality; and CVH, cardiovascular-related hospitalization.

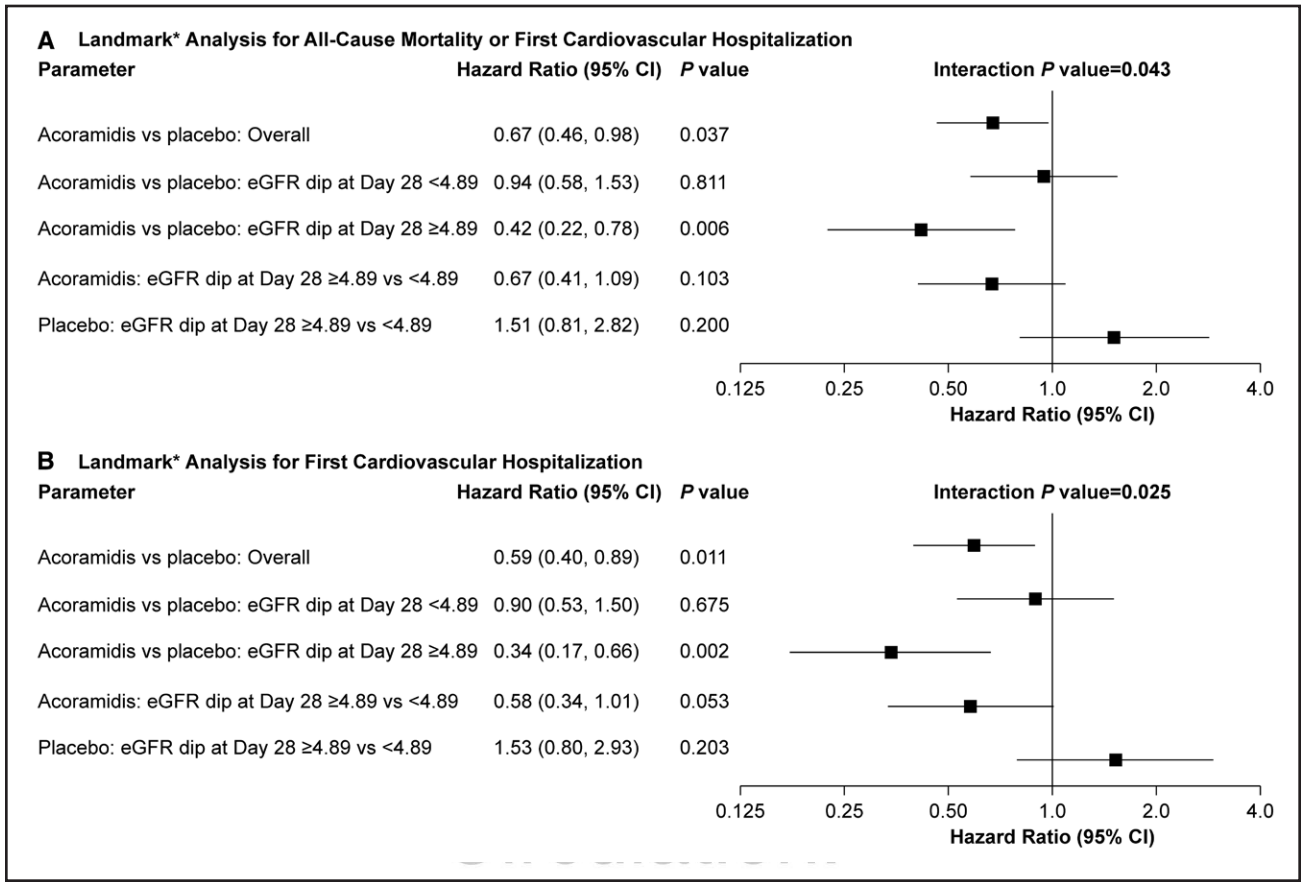

Figure 6. Subgroup analysis of cardiovascular-related hospitalization (CVH) and mortality outcomes based on estimated glomerular filtration rate (eGFR) dip at Day 28.
Forest plot of time-to-first event analyses for all-cause mortality (ACM) or CVH and for CVH alone from a 12-month analysis initiated at the Day 28 landmark in the intention-to-treat (ITT) population. The analysis compares the overall result of acoramidis vs placebo with subgroup analyses conducted between and within each treatment arm, according to an acute eGFR dip greater or less than the overall population median. The median dip from baseline in eGFR at Day 28 for the overall ITT population in ATTRibute-CM was 4.89 mL/min/1.73 m^2. Subgroups were defined by whether the magnitude of dip through Day 28 was above (greater than or equal to) or below (less than) this median. Cox proportional hazards models were used to estimate hazard ratios for ACM or first CVH and for first CVH alone, for the overall study population and for subgroups with an eGFR dip greater or less than the overall population median, between and within treatment arms. Interaction *P* values are for the interaction term between treatment group (acoramidis and placebo) and eGFR dip subgroup (<4.89 and ≥4.89 mL/min per 1.73 m^2). **A**, Forest plot of Cox proportional hazards analyses for the time-to-first event for ACM or CVH from a 12-month analysis initiated at the Day 28 landmark. **B**, Forest plot of Cox proportional hazards analyses for the time-to-first event for CVH from a 12-month analysis initiated at the Day 28 landmark. *12-month analysis initiated at Day 28 landmark.

no change or an acute increase in eGFR, rather than the observed acute dip.

Based on these considerations, the acute dip in eGFR following initiation of acoramidis may represent a beneficial kidney effect that could be relevant to the observed early separation between acoramidis and placebo in adverse clinical outcomes over the 12 months following the eGFR dip. Conversely, the absence of these effects in the placebo group would be associated with worse clinical outcomes within the first 12 months after Day 28. Although this post hoc analysis is hypothesis-generating, it provides impetus to explore this important association further in future studies.

The placebo-corrected treatment effect on the chronic eGFR slope reported here (2.47 mL/min per 1.73 m^2 per year for acoramidis) compares favorably with those of other established kidney therapeutics. Specifically in the setting of heart failure, prior trials have reported a difference versus placebo in the eGFR slope that, although clinically important, was of a smaller magnitude than that observed with acoramidis: 1.76 mL/min per 1.73 m^2 per year for dapagliflozin in heart failure with reduced ejection fraction,[15] 1.73 mL/min per 1.73 m^2 per year for empagliflozin in heart failure with reduced ejection fraction,[16] 1.36 mL/min per 1.73 m^2 per year for empagliflozin in heart failure with preserved ejection fraction,[17] and 0.2 mL/min per 1.73 m^2 per year for finerenone in heart failure with preserved ejection fraction.[18]

The hypothesis of a direct kidney effect with acoramidis (versus an indirect effect caused by better preservation of cardiac function) might be supported by reported clinical trial experiences with other ATTR therapies. In the

ATTR-ACT trial with the TTR stabilizer tafamidis, the profile of a beneficial effect presumably driven by a slower deterioration in heart failure severity was observed. Although there was no acute change in kidney function, a late separation from placebo in the eGFR slope emerged ≈18 months after therapy initiation. However, this observation might have been influenced by the composite nature of the end point described in this analysis, which included ACM, which was previously shown to begin to be evident at about 18 months as well.[19,20] These observations follow the predicted timeline of TTR stabilization-mediated cardiovascular effects, with a gradually widening difference in heart failure severity emerging between groups, accompanied by a slower worsening in kidney function compared with placebo.

Additional preliminary observations have recently been reported from the HELIOS-B trial of vutrisiran in ATTR-CM and the NEURO-TTRansform trial of eplontersen in ATTR polyneuropathy.[21,22] In these reports, neither an acute dip in eGFR nor any apparent population-level change in the chronic eGFR slope was observed.

The possibility of a unique renal property of acoramidis is supported in the current analysis by the ≈23% of participants who used concomitant tafamidis in the placebo arm of the ATTRibute-CM trial. In that analysis, tafamidis did not recapitulate the acute eGFR dip observed with acoramidis initiation, nor did it modify the chronic effect of acoramidis on the eGFR slope, in contrast to the observations with acoramidis, a drug with a similar primary mechanism of action (TTR stabilization). These data support the hypothesis that acoramidis may possess a direct mechanism of action influencing kidney function, resembling the pattern seen with drugs acting directly on the kidney, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and sodium-glucose cotransporter-2 inhibitors. Further studies are required to elucidate the specific mechanism(s) contributing to the influence of acoramidis on kidney function. For example, direct assessment of renal hemodynamics at the level of the glomerulus versus tubular solute handling, specifically alteration of natriuretic mechanisms, are potential avenues for further research.

Limitations

These are post hoc analyses of clinical trials that were not designed to study changes in kidney function. Consequently, there are several important limitations. Creatinine was the only filtration marker included in these trials, and changes from nonfiltration-related factors such as creatinine production or secretion could have affected the results. Thus, the absence of measurement of a marker such as cystatin C is a limitation. Given the long-term nature of the studies and unavoidable participant discontinuations in both ATTRibute-CM and its OLE, a survival bias affecting these observations cannot be excluded. During the ATTRibute-CM study, although concomitant use of tafamidis was permitted after Month 12, its use was at the discretion of the investigator and thus not standardized with respect to either the timing of initiation or the duration of concomitant use. The percentage of participants with tafamidis drop-in was higher in the placebo group than in the acoramidis group, which may have led to an underestimation of the effect of acoramidis on clinical outcomes. This limitation was addressed, in part, by using the 12-month landmark analysis. Our study did not explore the mechanism(s) underlying the effects of acoramidis treatment on kidney function and, as such, this is a high priority for additional prospective mechanistic studies.

Conclusions

Acoramidis treatment resulted in an acute, dose-dependent dip in eGFR, which was fully reversible and associated with both acute and chronic reductions in albuminuria and improvements in the chronic eGFR slope compared with placebo. The potentially unique mechanisms contributing to these observations are unknown. The lack of any observed effect of concomitant tafamidis use on kidney function in our trial suggests that the mechanism underlying the observed effects of acoramidis on kidney function may well be distinct from its primary mechanism of action—TTR stabilization. The observed acute dip and potential early influence on improved clinical cardiovascular outcomes in the first year have not previously been reported with other disease-modifying ATTR-CM therapies. Additional investigation is needed to further explore the mechanism(s) and therapeutic implications of these observations.

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REFERENCES

1. Rapezzi C, Quarta CC, Riva L, Longhi S, Gallelli I, Lorenzini M, Ciliberti P, Biagini E, Salvi F, Branzi A. Transthyretin-related amyloidoses and the heart: a clinical overview. *Nat Rev Cardiol*. 2010;7:398–408. doi: 10.1038/nrcardio.2010.67
2. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:2872–2891. doi: 10.1016/j.jacc.2019.04.003
3. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation*. 2012;126:1286–1300. doi: 10.1161/CIRCULATIONAHA.111.078915
4. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, Nair AP, Nativi-Nicolau J, Ruberg FL; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation*. 2020;142:e7–e22. doi: 10.1161/CIR.0000000000000792
5. Judge DP, Heitner SB, Falk RH, Maurer MS, Shah SJ, Witteles RM, Grogan M, Selby VN, Jacoby D, Hanna M, et al. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2019;74:285–295. doi: 10.1016/j.jacc.2019.03.012
6. BridgeBio Pharma, Inc. *Prescribing information, Attruby (acoramidis)*. FDA; 2024. Accessed June 11, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216540s000lbl.pdf
7. BridgeBio Europe B.V. *SmPC, Beyonttra (acoramidis)*. EMA; 2024. Accessed June 11, 2026. https://ec.europa.eu/health/documents/community-register/2025/20250210165087/anx_165087_en.pdf
8. Bayer plc. *SmPC, Beyonttra (acoramidis)*. MHRA; 2025. Accessed June 11, 2026. https://mhraproducts4853.blob.core.windows.net/docs/65cdc303a1411fa20142875b65739fad8ac72058
9. Alexion. *SmPC, Beyonttra (acoramidis)*. MHLW Japan; 2025. Accessed June 11, 2026. https://www.pmda.go.jp/files/000278404.pdf
10. Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S, Grogan M, Hanna M, Hoffman J, Masri A, et al. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2024;390:132–142. doi: 10.1056/NEJMoa2305434
11. Judge DP, Alexander KM, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs SDJ, Grogan M, Hanna M, Masri A, Maurer MS, et al. Efficacy of acoramidis on all-cause mortality and cardiovascular hospitalization in transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2025;85:1003–1014. doi: 10.1016/j.jacc.2024.11.042
12. Masri A, Judge DP, Ruberg FL, Gillmore JD, Grodin JL, Obici L, Maurer MS, Fontana M, Poulsen SH, van der Meer P, et al. Effect of acoramidis on recurrent and cumulative cardiovascular outcomes in ATTR-CM: exploratory analysis from ATTRibute-CM. *J Am Coll Cardiol*. 2026;87:490–501. doi: 10.1016/j.jacc.2025.09.013
13. Judge DP, Gillmore JD, Alexander KM, Ambardekar AV, Cappelli F, Fontana M, Garcia-Pavia P, Grodin JL, Grogan M, Hanna M, et al. Long-term efficacy and safety of acoramidis in ATTR-CM: initial report from the open-label extension of the ATTRibute-CM trial. *Circulation*. 2025;151:601–611. doi: 10.1161/CIRCULATIONAHA.124.072771
14. Vonesh E, Tighiouart H, Ying J, Heerspink HL, Lewis J, Staplin N, Inker L, Greene T. Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease. *Stat Med*. 2019;38:4218–4239. doi: 10.1002/sim.8282
15. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, Chopra V, de Boer RA, Desai AS, Ge J, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation*. 2021;143:298–309. doi: 10.1161/CIRCULATIONAHA.120.050391
16. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424. doi: 10.1056/NEJMoa2022190
17. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461. doi: 10.1056/NEJMoa2107038
18. Mc Causland FR, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, Henderson AD, Brinker M, Perkins R, Scheerer MF, et al. Finerenone and kidney outcomes in patients with heart failure: the FINEARTS-HF trial. *J Am Coll Cardiol*. 2025;85:159–168. doi: 10.1016/j.jacc.2024.10.091
19. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin

amyloid cardiomyopathy. *N Engl J Med.* 2018;379:1007–1016. doi: 10.1056/NEJMoa1805689
20. Sperry BW, Sultan MB, Gundapaneni B, Tai SS, Witteles RM. Effect of tafamidis on renal function in patients with transthyretin amyloid cardiomyopathy in ATTR-ACT. *JACC CardioOncol.* 2024;6:300–306. doi: 10.1016/j.jaccao.2024.02.007
21. Maurer MS, Gillmore JD, Berk JL, Masri A, da Silva MD, Kwoh J, Little DJ, Nåtman J, Zhou W, Waddington-Cruz M. Kidney function and proteinuria with eplontersen treatment for hereditary transthyretin amyloidosis. *J Card Fail.* 2025;31:346–347. doi: 10.1016/j.cardfail.2024.10.423
22. Sheikh F, Dang J, Fontana M, AUDARD V, Garcia-Pavia P, Khouri M, Jobbe-Duval A, Brailovsky Y, Zheng H, Eraly S, et al. Abstract 4362795: Vutrisiran improved outcomes versus placebo in patients with transthyretin amyloidosis with cardiomyopathy and severe chronic kidney disease: post hoc analysis of HELIOS-B. *Circulation.* 2025;152:A4362795. doi: 10.1161/circ.152.suppl_3.4362795