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RESEARCH ARTICLE

Outpatient worsening heart failure in transthyretin amyloid cardiomyopathy: findings from ATTRibute-CM

Marianna Fontana [1,*], Francesco Cappelli[2], Pablo Garcia-Pavia[3,4], Daniel P. Judge[5], Laura Obici [6], Ahmad Masri [7], João R. Agostinho[8,9], Carsten Tschöpe [10,11,12], Kai Vogtländer[13], Antonio Ciaccia[14], Ana Zazula[15], Stefan Zeitler[16], Jean-François Tamby[17], Jonathan C. Fox[17], Julian D. Gillmore [1], and Thibaud Damy [18]

[1]National Amyloidosis Centre, University College London, Royal Free Hospital, Rowland Hill Street, London NW3 2PF, UK; [2]Tuscan Referral Center for Amyloid Treatment, Department of Clinical and Experimental Medicine, Careggi University Hospital, Florence, Italy; [3]Department of Cardiology of Hospital Universitario Puerta de Hierro Majadahonda, IDIPHIM, CIBERCV, Madrid, Spain; [4]Divison of Inherited Cardiomyopathies, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; [5]Division of Cardiology, Medical University of South Carolina, Charleston, SC, USA; [6]Amyloidosis Research and Treatment Centre, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; [7]Division of Cardiovascular Medicine, Oregon Health & Science University, Portland, OR, USA; [8]Cardiology Department, Santa Maria University Center, Lisbon, Portugal; [9]CAML, CCUL@RISE, Lisbon, Portugal; [10]Department of Cardiology, Angiology and Intensive Medicine at Campus Virchow (CVK), Deutsches Herzzentrum der Charité (DHZC),Berlin, Germany; [11]Department of Cardiology, Berlin Institute of Health (BIH) at Charité—Center for Regenerative Therapies (BCRT), Berlin, Germany; [12]German Centre for Cardiovascular Research (DZHK), Partner Site Berlin, Charité University, Berlin, Germany; [13]Medical Affairs Statistics, Bayer AG, Wuppertal, Germany; [14]Bayer Inc, Mississauga, ON, Canada; [15]Bayer S.A., Sao Paulo, Brazil; [16]Bayer AG, Basel, Switzerland; [17]BridgeBio Pharma, Inc., SanFrancisco, CA, USA; and [18]Department of Cardiology, Referral Center for Cardiac Amyloidosis, Hôpital Henri-Mondor, Créteil, France

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Abstract

Background Acoramidis, an oral transthyretin stabilizer that achieves near-complete (≥90%) transthyretin stabilization, demonstrated significant clinical benefit over placebo in participants with transthyretin amyloid cardiomyopathy (ATTR-CM) in the phase 3 ATTRibute-CM trial (NCT03860935).

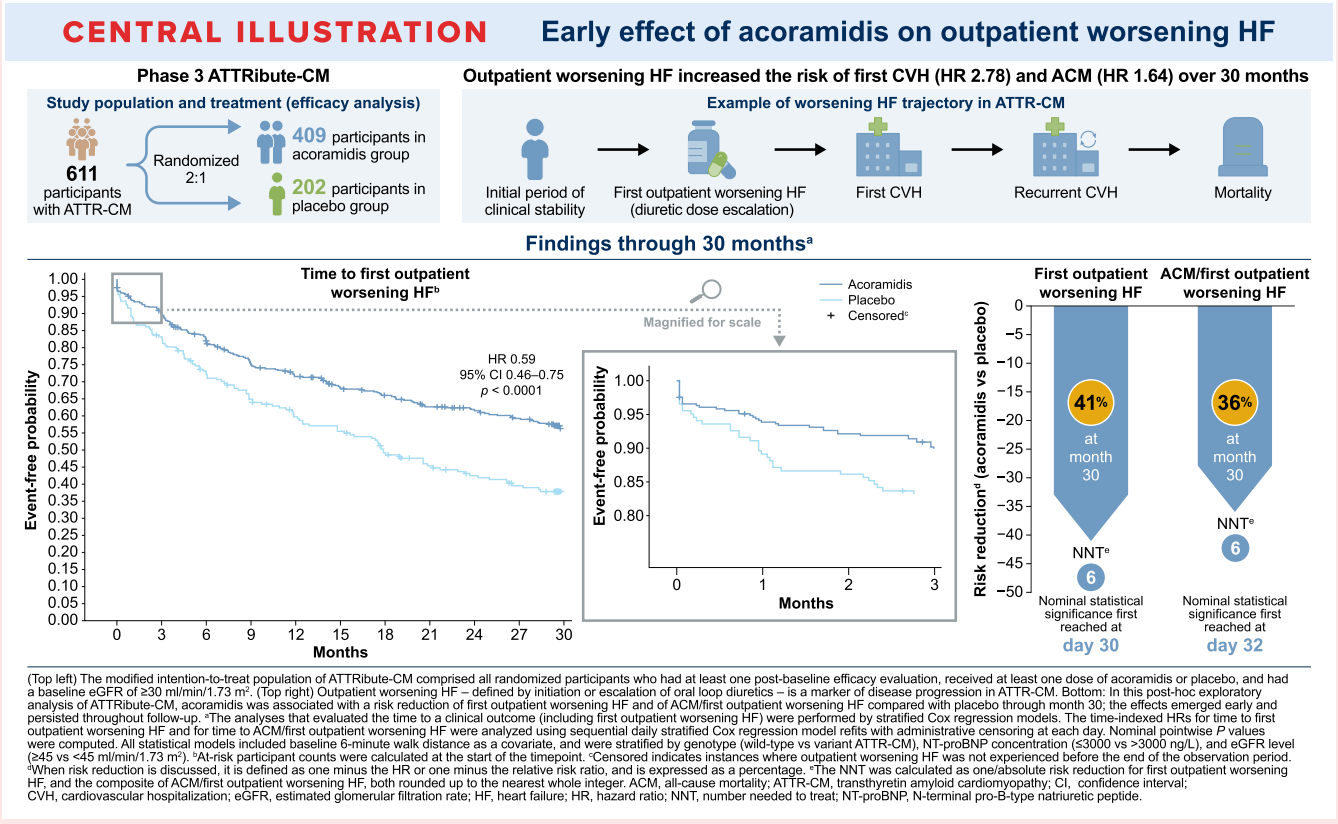
Methods Post-hoc exploratory analyses of ATTRibute-CM were performed to evaluate associations between outpatient worsening heart failure (HF) (initiation/escalation of oral loop diuretics) and clinical outcomes, the impact of acoramidis on outpatient worsening HF, and the effect of acoramidis on clinical outcomes adjusting for time-dependent first outpatient worsening HF.

Results In the modified-intention-to-treat population, 287/611 participants (46.97%) experienced outpatient worsening HF, which was associated with an increased risk of all-cause mortality (ACM)/recurrent cardiovascular hospitalization (CVH) (hazard ratio [HR] 1.95, 95% confidence interval [CI] 1.51–2.51), first CVH (HR 2.78, 95% CI 1.95–3.95), ACM (HR 1.64, 95% CI 1.14–2.36), and cardiovascular mortality (HR 1.63, 95% CI 1.08–2.46) through month 30. Acoramidis was associated with a 41% risk reduction of first outpatient worsening HF versus placebo (HR 0.59, 95% CI 0.46–0.75); Kaplan–Meier curves separated early, nominal statistical significance was first reached at day 30 (HR 0.562, 95% CI 0.317–0.998; $P = .0492$), and sustained nominal statistical significance was achieved at day 134 through month 30. When adjusting for time-dependent first outpatient worsening HF over 30 months, acoramidis reduced the risk of ACM/recurrent CVH and first CVH versus placebo.

Conclusions Outpatient worsening HF was associated with clinical outcomes in ATTR-CM. Acoramidis reduced the risk of outpatient worsening HF; effects emerged early and persisted throughout follow-up.

* Corresponding author. Tel: +44-207-433-2764, Email: m.fontana@ucl.ac.uk

Graphical abstract



(Top left) The modified intention-to-treat population of ATTRibute-CM comprised all randomized participants who had at least one post-baseline efficacy evaluation, received at least one dose of acoramidis or placebo, and had a baseline eGFR of ≥30 ml/min/1.73 m². (Top right) Outpatient worsening HF – defined by initiation or escalation of oral loop diuretics – is a marker of disease progression in ATTR-CM. Bottom: In this post-hoc exploratory analysis of ATTRibute-CM, acoramidis was associated with a risk reduction of first outpatient worsening HF and of ACM/first outpatient worsening HF compared with placebo through month 30; the effects emerged early and persisted throughout follow-up. [a]The analyses that evaluated the time to a clinical outcome (including first outpatient worsening HF) were performed by stratified Cox regression models. The time-indexed HRs for time to first outpatient worsening HF and for time to ACM/first outpatient worsening HF were analyzed using sequential daily stratified Cox regression model refits with administrative censoring at each day. Nominal pointwise *P* values were computed. All statistical models included baseline 6-minute walk distance as a covariate, and were stratified by genotype (wild-type vs variant ATTR-CM), NT-proBNP concentration (≤3000 vs >3000 ng/L), and eGFR level (≥45 vs <45 ml/min/1.73 m²). [b]At-risk participant counts were calculated at the start of the timepoint. [c]Censored indicates instances where outpatient worsening HF was not experienced before the end of the observation period. [d]When risk reduction is discussed, it is defined as one minus the HR or one minus the relative risk ratio, and is expressed as a percentage. [e]The NNT was calculated as one/absolute risk reduction for first outpatient worsening HF, and the composite of ACM/first outpatient worsening HF, both rounded up to the nearest whole integer. ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; CVH, cardiovascular hospitalization; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; NNT, number needed to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Transthyretin amyloid cardiomyopathy • Acoramidis • Outpatient worsening heart failure • Diuretic • Heart failure

Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive condition caused by destabilization and dissociation of transthyretin (TTR) tetramers into monomers, which misfold and accumulate as amyloid fibrils in the myocardial extracellular space.[1,2] The disease follows a progressive heart failure (HF) trajectory, in which episodes of worsening HF—managed in both outpatient and inpatient settings—are strongly associated with cardiovascular mortality (CVM) and therefore represent key markers of disease progression.[1,3–5]

Outcomes in ATTR-CM have improved in recent years with the introduction of disease-modifying TTR therapies and optimized HF management.[2,6,7] These advances have heightened interest in markers that sensitively reflect HF worsening and overall disease trajectory.[7,8] Outpatient worsening HF, defined as initiation or intensification of oral loop diuretics, is a strong independent predictor of mortality in HF and ATTR-CM.[4,8–12] Likewise, higher loop-diuretic requirements correlate with increased mortality risk.[9,13] Together, these findings support outpatient worsening HF as a robust marker of disease progression and a potential therapeutic target.

Acoramidis is an oral TTR stabilizer that achieves near-complete (≥90%) TTR stabilization, and is approved for the treatment of wild-type and variant ATTR-CM in the United States, European Union, Japan, United Kingdom, and Switzerland.[14–19] In the phase 3 ATTRibute-CM trial (NCT03860935), acoramidis significantly improved outcomes versus placebo across the prespecified hierarchical endpoint—including mortality, cardiovascular hospitalization (CVH, which included urgent HF visits that required intravenous diuretic therapy), N-terminal pro–B-type natriuretic peptide (NT-proBNP), and 6-minute walk distance—through month 30 ($P < .001$), with a favourable safety profile.[20]

In subsequent analyses, acoramidis reduced the occurrence of all-cause mortality (ACM)/first CVH by 36%, ACM and recurrent CVH by 42%, and the annual frequency of CVH by 50%.[21] In addition, acoramidis was associated with early and sustained reductions in ACM/first CVH events and recurrent CVH events, with separation of Kaplan–Meier curves at month 3 and at month 1, respectively, and maintained through month 30.[3,21] In the ATTRibute-CM open-label extension study (NCT04988386), continuous use of acoramidis was associated with a reduced risk of ACM/first CVH at month 42 versus participants who had switched from placebo to acoramidis at month 30.[22] As acoramidis leads to near-complete TTR stabilization and has an effect on estimated glomerular filtration rate (eGFR) that is consistent with a renal haemodynamic effect,[14,16] acoramidis may also influence earlier manifestations of HF deterioration, such as outpatient diuretic escalation.

In this *post hoc* analysis, we evaluated: (1) the prognostic significance of outpatient worsening HF, (2) the effect of acoramidis on outpatient worsening HF, and (3) whether the effects of acoramidis persist for clinical outcomes after adjusting for time-dependent outpatient worsening HF.

Methods

Study design

The methodology of the ATTRibute-CM study has previously been described.[20] In brief, ATTRibute-CM was a randomized, double-blind, placebo-controlled trial, in which 632 participants were assigned in a 2:1 ratio to receive either acoramidis 800 mg twice daily or placebo for 30 months.

Eligible participants were adults aged 18–90 years with an established diagnosis of chronic, stable, and symptomatic ATTR-CM; New York Heart Association (NYHA) functional class I, II, or III; and either a wild-type or variant TTR genotype. The efficacy analyses were carried out in the modified intention-to-treat (mITT) population, which comprised all randomized participants who had at least one post-baseline efficacy evaluation, received at least one dose of acoramidis or placebo, and had a baseline eGFR of ≥30 ml/min/1.73 m^2. Safety and tolerability were evaluated in the safety population, which consisted of all randomized participants who received at least one dose of acoramidis or placebo. At the discretion of the investigator, participants could initiate open-label concomitant tafamidis at month 12.

ATTRibute-CM was conducted in accordance with the International Conference on Harmonization 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.

Outpatient worsening heart failure

Data on diuretics were collected at baseline and throughout the study. Outpatient worsening HF was defined as any post-baseline increase in loop-diuretic dose in relation to the baseline value and any new initiation among participants who were not taking loop diuretics at baseline. Daily oral loop-diuretic doses were converted to the furosemide-equivalent dose as follows: bumetanide 1 mg or torsemide 20 mg = furosemide 40 mg.[13] Changes in oral loop-diuretic therapy were permitted throughout the study at the investigator's discretion and captured at every study visit.

Association between outpatient worsening heart failure and clinical endpoints

Analyses were carried out in the mITT population to evaluate the associations between outpatient worsening HF and clinical endpoints (ACM/recurrent CVH, first CVH, ACM, and CVM). The full definitions of these clinical endpoints have been described previously.[3,21] Clinical endpoints were assessed every 90 days through month 30.

Treatment effect of acoramidis on outpatient worsening heart failure

Analyses were carried out in the mITT population to assess the impact of acoramidis on the rate and risk of outpatient worsening HF, and to describe event-free survival of a composite endpoint of ACM/first outpatient worsening HF, furosemide-equivalent dose at different time points, total furosemide-equivalent dose at the time of the first outpatient worsening HF, and the proportion of participants who received a total daily furosemide-equivalent dose over time.

Treatment effect of acoramidis on clinical outcomes adjusting for outpatient worsening heart failure

An analysis was performed to investigate the treatment effect of acoramidis on clinical outcomes when adjusted for outpatient worsening HF as a time-dependent covariate over 30 months.

Treatment-emergent adverse events

Treatment-emergent adverse events were evaluated in the context of outpatient worsening HF in the safety population.

Statistical analysis

The present analyses are exploratory and use data on participant concomitant medication as documented during ATTRibute-CM. The daily dose of oral loop-diuretic therapy was computed if the tablet dosage and daily intake frequency were documented. The analyses excluded documented episodes of oral loop diuretic administration with ambiguous information that did not allow for the calculation of a participant's total daily dose.

The analyses that evaluated the time to a clinical outcome (including first outpatient worsening HF) were performed by stratified Cox regression models. If the first outpatient worsening HF is not part of an endpoint, then it was included as a time-dependent covariate in the model. Randomized treatment was another covariate used to evaluate the effect of acoramidis.

In the analysis that evaluated the association between outpatient worsening HF and ACM/recurrent CVH, we used the Andersen–Gill extension of the Cox regression with a robust sandwich estimate for the covariance matrix for recurrent CVH.

The time-indexed HRs for time to first outpatient worsening HF and for time to ACM/first outpatient worsening HF were analysed using sequential daily stratified Cox regression model refits with administrative censoring at each day. Nominal pointwise *P* values were computed.

All statistical models included baseline 6-minute walk distance as a covariate and were stratified by genotype (wild-type vs variant ATTR-CM), NT-proBNP concentration (≤3000 vs >3000 ng/L), and eGFR level (≥45 vs <45 ml/min/1.73 m^2). The models used for the association of outpatient worsening HF and clinical outcomes were additionally stratified by randomized treatment. When risk reduction is discussed, it is defined as one minus the hazard ratio (HR) or one minus the relative risk ratio and is expressed as a percentage. The number-needed-to-treat (NNT) was calculated as one/absolute risk reduction for first outpatient worsening HF, and the composite of ACM/first outpatient worsening HF, both rounded up to the nearest whole integer.

Results

Baseline characteristics

In ATTRibute-CM, 632 participants underwent randomization (safety population): 421 in the acoramidis group and 211 in the placebo group. The mITT population included 611 participants who received acoramidis ($n = 409$) or placebo ($n = 202$).

Baseline demographic and clinical characteristics of the mITT population have been reported previously.[20] Briefly, characteristics were comparable between treatment groups and represented a contemporary, global population of patients with ATTR-CM.[20] In addition, baseline characteristics were generally well balanced between participants with and without outpatient worsening HF (Supplementary Table S1). As expected, those who experienced outpatient worsening HF were slightly more symptomatic at baseline (higher NYHA class), had marginally lower Kansas City Cardiomyopathy Questionnaire overall summary scores, and had modestly higher NT-proBNP values. Use of background HF therapies was similar between groups.

Clinical outcomes in participants with outpatient worsening heart failure

In the overall mITT population ($n = 611$), 287 participants (46.97%) had outpatient worsening HF. First outpatient worsening HF was associated with a greater risk of ACM/recurrent CVH (HR 1.95, 95% confidence interval [CI] 1.51–2.51; $P < .0001$), first CVH (HR 2.78, 95% CI 1.95–3.95; $P < .0001$), ACM (HR 1.64, 95% CI 1.14–2.36; $P = .0083$), and CVM (HR 1.63, 95% CI 1.08–2.46; $P = .0197$) through month 30 (*Figure 1*).

Impact of acoramidis on outpatient worsening heart failure

During the double-blind period, a lower proportion of participants treated with acoramidis experienced outpatient worsening HF (167/409 [40.83%]) compared with those who received placebo (120/202 [59.41%]).

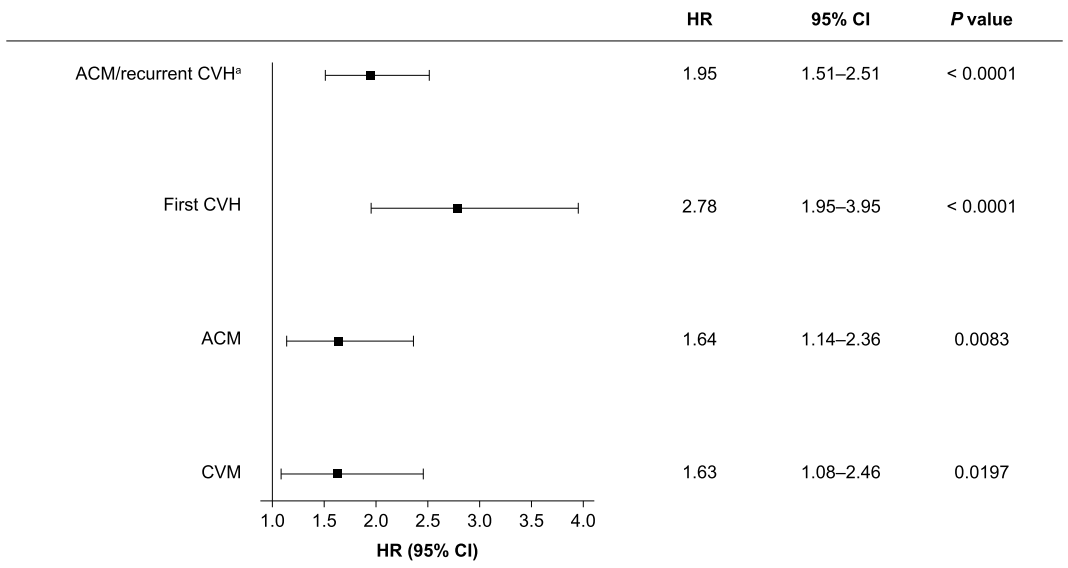


Figure 1 Associations between first outpatient worsening HF and clinical endpoints. Analysis carried out in the mITT population. HRs for the association between first outpatient worsening HF and endpoints were analysed using a Cox regression model with baseline 6MWD as a covariate, and stratified by randomized treatment and randomization stratification factors, including genotype (wild-type vs variant ATTR-CM), NT-proBNP concentration (≤3000 vs >3000 ng/L), and eGFR level (≥45 vs <45 ml/min/1.73 m^2), which were based on information from the interactive voice/web response system at screening. An HR of >1.00 indicates greater risk with outpatient worsening HF. [a]Andersen–Gill extension of the Cox regression with robust sandwich estimate for the covariance matrix for recurrent CVH. 6MWD, 6-minute walking distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloid cardiomyopathy; CI, confidence interval; CVH, cardiovascular hospitalization; CVM, cardiovascular mortality; eGFR, estimated glomerular filtration rate; HR, hazard ratio; mITT, modified intention-to-treat; NT-proBNP, N-terminal pro–B-type natriuretic peptide

Table 1 Effect of acoramidis versus placebo on outpatient worsening HF

n (%)	Acoramidis (*n* = 409)	Placebo (*n* = 202)	HR (95% CI); *P* value
Outpatient worsening HF events			
Participants with ≥1 event	167 (40.8)	120 (59.4)	0.59 (0.46–0.75); <0.0001
Frequency of outpatient worsening HF events			
Participants with 1 event	80 (19.6)	53 (26.2)	
Participants with 2 events	32 (7.8)	28 (13.9)	
Participants with 3 events	18 (4.4)	11 (5.4)	
Participants with ≥4 events	37 (9.0)	28 (13.9)	

CI, confidence interval; HF, heart failure; HR, hazard ratio

The proportion of participants treated with acoramidis was also lower across outpatient worsening HF event frequency categories (1, 2, 3, and ≥4) versus those who received placebo (*Table 1*). Based on an absolute risk reduction of 18.58% with acoramidis versus placebo, the NNT to prevent first outpatient worsening HF over 30 months of treatment was six.

In a time-to-first event analysis, acoramidis was associated with a 41% risk reduction of first outpatient worsening HF (HR 0.59, 95% CI 0.46–0.75; $P < .0001$) relative to placebo, with the Kaplan–Meier curves separating early (*Figure 2*). Nominal statistical significance was first reached at day 30 (HR 0.562, 95% CI 0.317–0.998; $P = .0492$); sustained nominal statistical significance was achieved at day 134 through month 30 (Supplementary Figure S1).

In the analysis for time to event-free survival for the composite endpoint of ACM/first outpatient worsening HF, acoramidis was associated with a 36% risk reduction of the composite endpoint (HR 0.64, 95% CI 0.52–0.79; $P < .0001$) relative to placebo, with the Kaplan–Meier curves separating early (*Figure 3*). Nominal statistical significance was first reached at day 32 (HR 0.56, 95% CI 0.32–0.98; $P = .0423$); sustained nominal statistical significance was achieved at day 137 through month 30. ACM/first outpatient worsening HF occurred in 52.08% of patients in the acoramidis group and 69.31% of patients in the placebo group. Based on an absolute risk reduction of 17.23% with acoramidis versus placebo, the NNT to prevent ACM/first outpatient worsening HF over 30 months of treatment was six.

The furosemide-equivalent dose increase from baseline to month 30 was lower among participants treated with acoramidis compared with those who received placebo. The mean (standard deviation) dose increased from 64.37 (62.64) mg at baseline to 82.88 (94.94) mg at month 30 in the acoramidis group and from 71.83 (64.79) mg at baseline to 98.71 (83.06) mg at month 30 in the placebo group. The median (minimum, maximum) dose was 40.00 (10, 400) mg at baseline and 40.00 (10, 600) mg at month 30 in the acoramidis group, and increased from 50.00 (10, 400) mg at baseline to 80.00 (20, 500) mg at month 30 in the placebo group (Supplementary Table S2).

In participants who experienced outpatient worsening HF, the total daily furosemide-equivalent dose at the time of the first outpatient

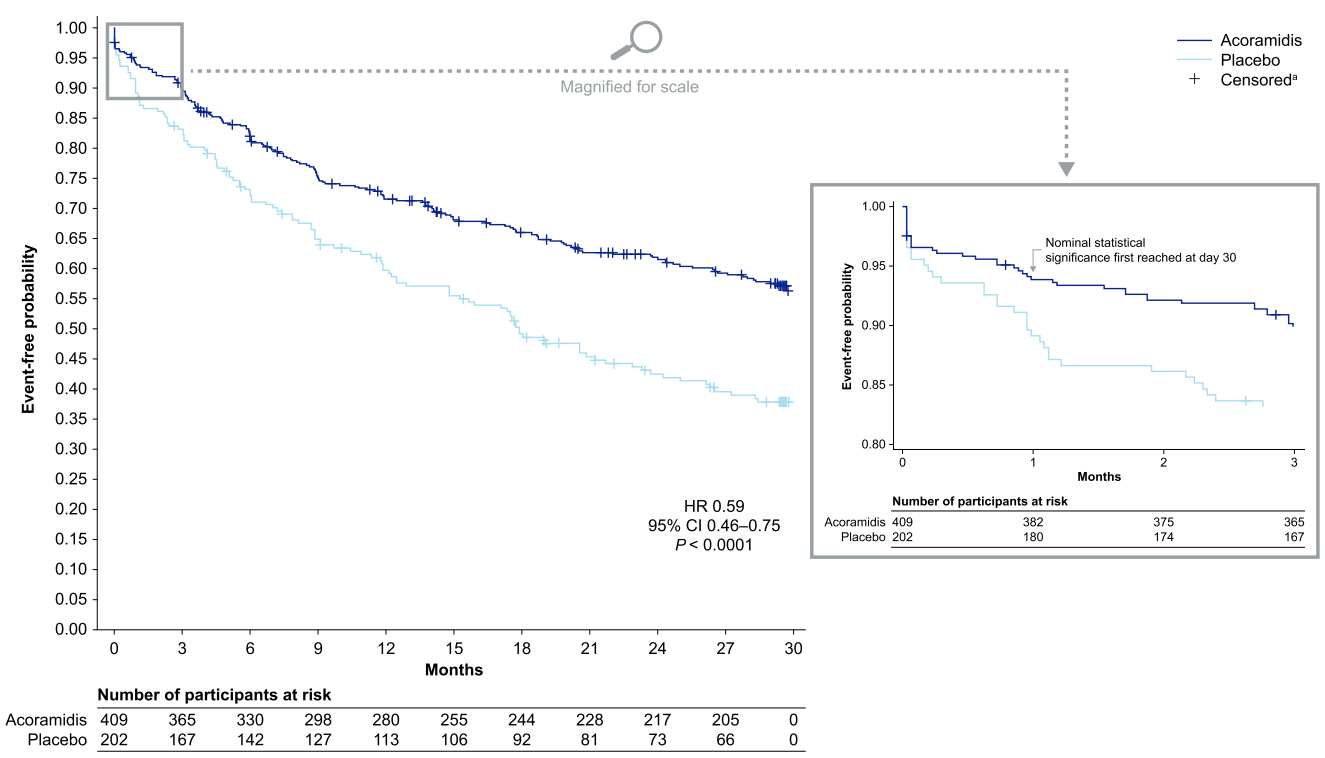


Figure 2 Kaplan–Meier curve for the time to first outpatient worsening HF through month 30. Analysis carried out in the modified intention-to-treat population. At-risk participant counts were calculated at the start of the timepoint. [a]Censored indicates instances where outpatient worsening HF was not experienced before the end of the observation period. CI, confidence interval; HF, heart failure; HR, hazard ratio

worsening HF was lower in participants treated with acoramidis than those who received placebo (Supplementary Table S3). A greater proportion of participants in the placebo group required total daily furosemide-equivalent doses of >120 mg compared with those in the acoramidis group over time (Supplementary Figure S2). The most commonly prescribed loop diuretic was furosemide, followed by bumetanide and torsemide (Supplementary Table S4).

Effect of acoramidis on clinical outcomes adjusted for outpatient worsening heart failure

Compared with placebo, acoramidis reduced the risk of ACM/recurrent CVH (HR 0.59, 95% CI 0.45–0.77; $P = .0001$) and first CVH (HR 0.63, 95% CI 0.45–0.88; $P = .0072$) after adjusting for first outpatient worsening HF as a time-dependent covariate over 30 months. There was a trend towards a lower risk of ACM (HR 0.82, 95% CI 0.57–1.17; $P = .2697$) and CVM (HR 0.75, 95% CI 0.50–1.12; $P = .1546$) with acoramidis versus placebo; however, the difference was not statistically significant.

Safety profile in the context of outpatient worsening heart failure

In the analysis of treatment-emergent adverse events in the context of outpatient worsening HF, the safety profile of acoramidis was generally favourable compared with placebo (Supplementary Table S5).

Discussion

In this analysis of ATTRibute-CM, outpatient worsening HF was common and associated with increased risks of clinical outcomes, despite only modest baseline differences between those with and without outpatient worsening HF. Acoramidis was associated with a reduced risk of outpatient worsening HF, with the Kaplan–Meier curves for first outpatient worsening HF separating early. Nominal statistical significance was first reached at day 30 and sustained nominal statistical significance was achieved at day 134 through month 30; in addition, acoramidis was associated with smaller increases in loop-diuretic requirements versus placebo. Importantly, the effects of acoramidis on ACM/recurrent CVH and first CVH persisted even after adjusting for outpatient worsening HF as a time-dependent covariate, and the safety profile of acoramidis remained favourable. These findings support outpatient worsening HF as a potential marker of disease progression and highlight the early and sustained clinical effects of acoramidis.

Outpatient worsening HF, typically defined by initiation or intensification of oral loop diuretics, is well established as a marker of adverse prognosis in HF populations and has been validated as an independent predictor of mortality in ATTR-CM.[4,8–12] In this analysis, outpatient worsening HF was consistently linked to increased risk across all major clinical endpoints, including ACM/recurrent CVH, first CVH, ACM, and CVM. The association with these endpoints persisted after adjusting for baseline 6-minute walk distance, which supports the concept that outpatient diuretic escalation reflects true clinical worsening and carries prognostic information beyond traditional assessments.

In the present analysis, acoramidis was associated with a lower incidence and risk reduction of outpatient worsening HF. This builds upon the previously reported effects of acoramidis on downstream events in

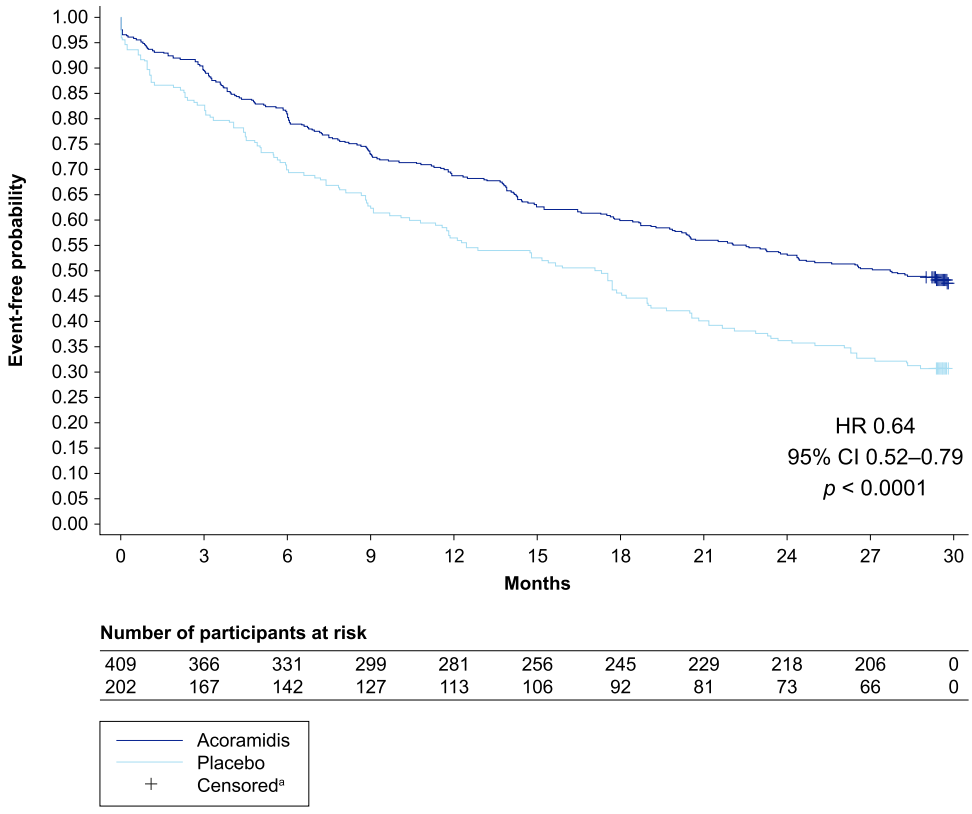


Figure 3 Kaplan–Meier curve for time to event-free survival of ACM/first outpatient worsening HF. Analysis carried out in the modified intention-to-treat population. At-risk participant counts were calculated at the start of the timepoint. [a]Censored indicates instances where ACM/first outpatient worsening HF did not occur before the end of the observation period. ACM, all-cause mortality; CI, confidence interval; HF, heart failure; HR, hazard ratio

the HF trajectory, including recurrent CVH and ACM/first CVH.[3,21] In addition, we found that the Kaplan–Meier curves for time to first outpatient worsening HF separated early, with nominal statistical significance reached at day 30 and sustained nominal statistical significance achieved at day 134 through month 30. These results extend the previously reported early effect of acoramidis on the cumulative incidence of CVM/recurrent CVH observed at month 1.[3]

A reduction in outpatient worsening HF has been observed in other phase 3 ATTR-CM clinical trials, but not until later timepoints.[7,23] In HELIOS-B (NCT04153149), vutrisiran reduced the risk of first outpatient worsening HF by 27% (HR 0.73, 95% CI 0.59–0.91) and recurrent events by 34% compared with placebo (relative rate ratio 0.66, 95% CI 0.56–0.78) during the double-blind period of up to 36 months.[23] In APOLLO-B (NCT03997383), the risk of outpatient worsening HF was reduced by 23% with patisiran versus placebo (HR 0.77, 95% CI 0.54–1.1) during the double-blind period of 12 months.[24] These findings provide additional context for the evaluation of outpatient worsening HF as a clinically relevant endpoint in ATTR-CM trials. Differences in study design, patient populations, and endpoint definitions should be considered when interpreting results across studies. The mechanism underlying the observed early effect of acoramidis is not fully defined; however, outpatient worsening HF may reflect subtle haemodynamic changes that precede overt decompensation.[12,25,26] In addition, the reduced need for loop-diuretic escalation among participants treated with acoramidis is consistent with mitigation of early HF instability. Participants who received acoramidis also progressed more slowly to higher diuretic doses, which suggests an attenuation in the trajectory of congestion-related deterioration. While there was a small difference in the median oral furosemide-equivalent dose at baseline between acoramidis and placebo groups (10 mg), this is unlikely to be clinically meaningful and have impacted outpatient worsening HF.

Of note, the effects of acoramidis on ACM/recurrent CVH and first CVH remained evident after adjusting for outpatient worsening HF as a time-dependent covariate, which indicates that the treatment effect on clinical outcomes is not solely mediated through prevention of outpatient decompensation. This suggests broader consequences of near-complete TTR stabilization on disease progression. The consistent separation of event-free survival curves for ACM/first outpatient worsening HF additionally suggests that this composite may have potential utility as an endpoint in future studies, as it may capture earlier manifestations of worsening HF that precede major clinical events.

Together, these findings support published data on the prognostic importance of outpatient worsening HF in ATTR-CM,[4,8,9] and indicate that acoramidis favourably influences both early and downstream components of the HF trajectory. Further work is warranted to elucidate the mechanistic basis of the very early divergence observed and to explore how outpatient worsening HF might complement traditional endpoints to provide a more comprehensive assessment of treatment effects.

These findings have implications for clinical trial design in ATTR-CM. Outpatient worsening HF represents an early, actionable clinical event that typically occurs upstream of HF hospitalizations and mortality.[25] As such, capturing this event may offer a more complete representation of the HF spectrum, from initial decompensation that requires diuretic intensification to recurrent CVH and terminal events. Incorporation of outpatient worsening HF into composite endpoints alongside CVH

and mortality may enhance sensitivity to early therapeutic effects, facilitate shorter and more pragmatic trial designs, and better reflect the day-to-day disease burden experienced by patients.

Limitations

Study limitations should be considered when interpreting these data. These include the competing risk of mortality and survival bias as participants who died early were not at risk of experiencing subsequent events, whereas participants who survived throughout the duration of ATTRibute-CM were more likely to accrue events. Therefore, the true effect of acoramidis on outpatient worsening HF and HF-related events may be underestimated due to survival bias. In addition, a higher proportion of patients in the placebo group (22.8%) received tafamidis from month 12 compared with those in the acoramidis group (14.9%),[20] which may have attenuated the observed treatment benefit with acoramidis.

Conclusions

In this post-hoc analysis of ATTRibute-CM, outpatient worsening HF was associated with an increased risk of ACM/recurrent CVH, first CVH, ACM, and CVM in participants with ATTR-CM. With acoramidis versus placebo, a reduced risk of outpatient worsening HF was observed, with effects emerging early and persisting through follow-up. After adjusting for time-dependent outpatient worsening HF, acoramidis reduced the risk of ACM/recurrent CVH and first CVH versus placebo. These results highlight the potential benefit of prompt treatment initiation following a diagnosis of ATTR-CM. Given the exploratory and post-hoc nature of these analyses, these findings warrant confirmation in further studies.

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Supplementary data

Supplementary data are available at *European Journal of Heart Failure* online.

Declarations

Disclosure of Interest

M.F. reports consultancy for Alexion/Caelum Biosciences, Alnylam, AstraZeneca, Attralus, Bayer, BridgeBio/Eidos, Cardior, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Lexeo Therapeutics, Mycardium, Novo Nordisk, Pfizer, Prothena; research grants from Alnylam, AstraZeneca, BridgeBio, Pfizer; share options in Lexeo Therapeutics; and shares in Mycardium. F.C. has acted as a consultant, advisor, or speaker for Alnylam Pharmaceuticals, AstraZeneca, Bayer, Bristol Myers Squibb, Eidos Therapeutics (a BridgeBio company), Novo Nordisk, and Pfizer. P.G.-P. has received speaker fees from Alnylam Pharmaceuticals, AstraZeneca, Bayer, Eidos Therapeutics (a BridgeBio company), Intellia Therapeutics, Ionis Pharmaceuticals, Novo Nordisk, and Pfizer; has received consulting fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Bayer, BridgeBio, Intellia Therapeutics, Ionis Pharmaceuticals, Pfizer, Neuroimmune, and Novo Nordisk; and has received research/educational support to his institution from Alnylam Pharmaceuticals, AstraZeneca, Bayer, BridgeBio, Intellia, Novo Nordisk, and Pfizer. D.P.J. has received consultancy fees from Alexion, Alnylam Pharmaceuticals, Attralus, Bayer, Cytokinetics, Eidos Therapeutics (a BridgeBio company), Lexeo Therapeutics, Novo Nordisk, Rocket Pharmaceuticals, and Tenaya Therapeutics. L.O. has acted as a consultant, advisor, and speaker for Alnylam Pharmaceuticals, AstraZeneca, Eidos Therapeutics (a BridgeBio company), Ionis Pharmaceuticals, Novo Nordisk, Pfizer, and Sobi, Inc. A.M. has received research grants from Attralus, Cytokinetics, Ionis, Janssen, and Pfizer; and personal consulting fees from Akros, Alexion, Alnylam, AstraZeneca, Attralus, Avidity, BioMarin, Bristol Myers Squibb, BridgeBio, Cytokinetics, Edgewise, Haya, Ionis, Lexeo, Lexicon, Neurimmune, Prothena, Pfizer, Rocket, and Tenaya. J.R.A. has received speaker and consulting fees from Alnylam Pharmaceuticals, AstraZeneca, Bayer, Bial, Boehringer Ingelheim & Lilly, Novartis, Pfizer, and Prothena Biosciences. C.T. has served as a consultant for *Cardiol Therapeutics* and Bayer Health; and has received honoraria from AstraZeneca, Pfizer, and Novartis. K.V., A.C., A.Z., and S.Z. are employees and stockholders of Bayer. J.-F.T. and J.C.F. are employees and stockholders of BridgeBio. J.D.G. has received consultancy fees from Alexion, Alnylam Pharmaceuticals, AstraZeneca, Attralus, Eidos Therapeutics (a BridgeBio company), Ionis, Intellia, and Pfizer, and is in receipt of institutional research grants from Alnylam and AstraZeneca. T.D. has received consulting fees from Alnylam, GlaxoSmithKline, Pfizer, and Prothena; honoraria from Alnylam, Pfizer, and Prothena; research grants from GlaxoSmithKline and Pfizer; and clinical trial support from Alnylam, Ionis Pharmaceuticals, and Pfizer.

Data Availability

Qualified academic investigators may submit requests for access to participant-level clinical data from BridgeBio-sponsored studies at MedInfo@BridgeBio.com. Requests for access to study data will be evaluated by BridgeBio Pharma, Inc., and access will be provided contingent on the approval of a research or study proposal and the execution of a data sharing agreement. BridgeBio Pharma will consider requests for access to participant-level data if participant privacy is ensured through methods such as data deidentification, pseudonymization, or anonymization (as required by applicable law) and if such disclosures were included in the informed consent form or study protocol of the relevant study.

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

ClinicalTrials.gov registration: NCT03860935.

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