ACORAMIDIS REDUCES ALL-CAUSE MORTALITY (ACM) AND CARDIOVASCULAR-RELATED HOSPITALIZATION (CVH): INITIAL OUTCOMES FROM THE ATTRibute-CM OPEN-LABEL EXTENSION (OLE) STUDY

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIPS WITH INDUSTRY

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ATTRibute-CM (ClinicalTrials.gov Identifier: NCT03860935) and the Open-Label Extension (ClinicalTrials.gov Identifier: NCT04988386) studies are sponsored by BridgeBio Pharma, Inc., San Francisco, CA

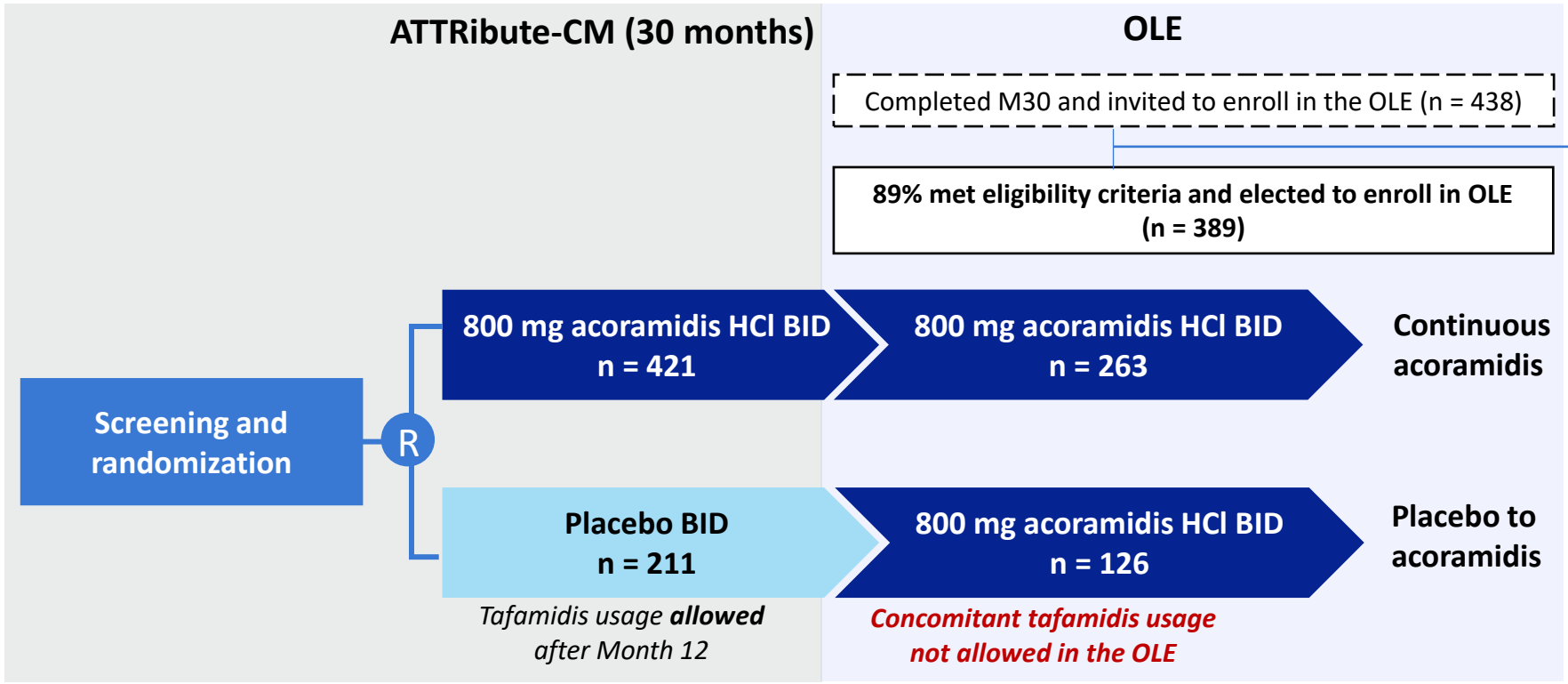
INTRODUCTION

- ATTR-CM is a progressive cardiomyopathy resulting in substantial cardiovascular morbidity and mortality caused by destabilization of the TTR tetramer[1,2]
- Acoramidis is an investigational, selective TTR stabilizer for the treatment of patients with ATTR-CM that achieves near-complete TTR stabilization (≥ 90%)[3,4]
- In the phase 3 ATTRibute-CM study, acoramidis led to a statistically significant improvement versus placebo in the four-step primary hierarchical endpoint of ACM, CVH, NT-proBNP levels, and 6MWD[5]
- In ATTRibute-CM, at Month 30, acoramidis led to significant reductions in the risk of ACM or first CVH, versus placebo[5,6]

OBJECTIVE:
To assess the long-term effects of acoramidis treatment on ACM and CVH in participants with ATTR-CM up to Month 42 in the ongoing ATTRibute-CM open-label extension (OLE) study

OLE: ClinicalTrials.gov NCT04988386; Available at: https://clinicaltrials.gov/study/NCT04988386?intr=acoramidis&rank=4 (accessed November 7, 2024).
6MWD, 6-minute walk distance; ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis cardiomyopathy; CVH, cardiovascular-related hospitalization; NT-proBNP, N-terminal pro–B-type natriuretic peptide; OLE, open-label extension study; TTR, transthyretin.
1. Rapezzi C, *et al. Nat Rev Cardiol* 2010;7(7):398–408; 2. Ruberg FL, *et al. JAMA* 2024;331(9):778–91; 3. Penchala SC, *et al. Proc Natl Acad Sci USA* 2013;110(24):9992–7; 4. Judge DP, *et al. J Am Coll Cardiol* 2019;74(3):285–95;
5. Gillmore JD, *et al. N Eng J Med* 2024;390:132–42; 6. Judge DP, *et al.* Manuscript under review

ATTRibute-CM AND OLE STUDY DESIGN, UP TO 42 MONTHS



Key OLE endpoints

Primary

- Long-term safety and tolerability

Secondary

- Time-to-first event for ACM, ACM or First CVH, and First CVH[a–c]
- ACM or recurrent CVH events[b–d]

Key ATTRibute-CM eligibility criteria

- Confirmed ATTR-CM diagnosis (wildtype or variant)
- Heart failure NYHA Class I–III

RCT primary endpoint

Key OLE eligibility criteria

- Completed 30 months of study treatment in ATTRibute-CM
- Discontinued tafamidis, if in use, before OLE entry
- No planned tafamidis or other investigational treatment for ATTR-CM during OLE

[a]Cox proportional hazards model. [b]ACM includes death from any cause, heart transplant, implantation of a cardiac mechanical assist device. [c]CVH was defined as a non-elective admission to an acute care setting for cardiovascular-related morbidity that resulted in at least a 24 hour stay, or an unplanned visit to an emergency department/ward, urgent care clinic, or day clinic of fewer than 24 hours for the management of decompensated heart failure requiring treatment with an intravenous diuretic. [d]Negative Binomial Regression Analysis.
ACM, all-cause mortality; ATTR-CM, transthyretin amyloidosis cardiomyopathy; BID, twice daily; CVH, cardiovascular-related hospitalization; M, month; NYHA, New York Heart Association; OLE, open-label extension; RCT, randomized controlled trial.

PARTICIPANTS AT ENTRY TO THE OLE

Participant characteristics[a,b]	Continuous acoramidis n = 263	Placebo to acoramidis n = 126
Age, years, mean (SD)[c]	78.8 (6.50)	79.7 (6.33)
Male sex, n (%)	244 (92.8)	115 (91.3)
ATTRwt-CM, n (%)[d]	242 (92.0)	120 (95.2)
ATTR-CM duration at randomization,[d,e] years, n Mean (SD)	 262 1.2 (1.10)	 126 1.1 (1.29)
NYHA class, n (%)[f] I or II III IV	 216 (82.1) 44 (16.7) 3 (1.1)	 79 (62.7) 45 (35.7) 1 (0.8)
NT-proBNP, pg/mL, n Median (IQR)	 252 2064.0 (1240.5, 3442.5)	 121 2905.0 (1624.0, 5087.0)
Serum TTR, mg/dL, n Mean (SD)	 253 32.8 (6.27)	 120 25.6 (6.61)
Participants who received tafamidis in the ATTRibute-CM study, n (%)	29 (11.0)	23 (18.3)

[a]Data are for all participants who enrolled in the OLE and received at least one dose of open-label acoramidis. [b]Baseline values are the last non-missing assessment values completed before the first OLE acoramidis treatment. [c]Age calculated from the first OLE treatment date and date of birth/age. [d]Data at the time of randomization in ATTRibute-CM (not at OLE entry). [e]Calculated as (randomization date – date of ATTR-CM diagnosis)/365.25. [f]Data missing for one patient in the placebo to acoramidis group.

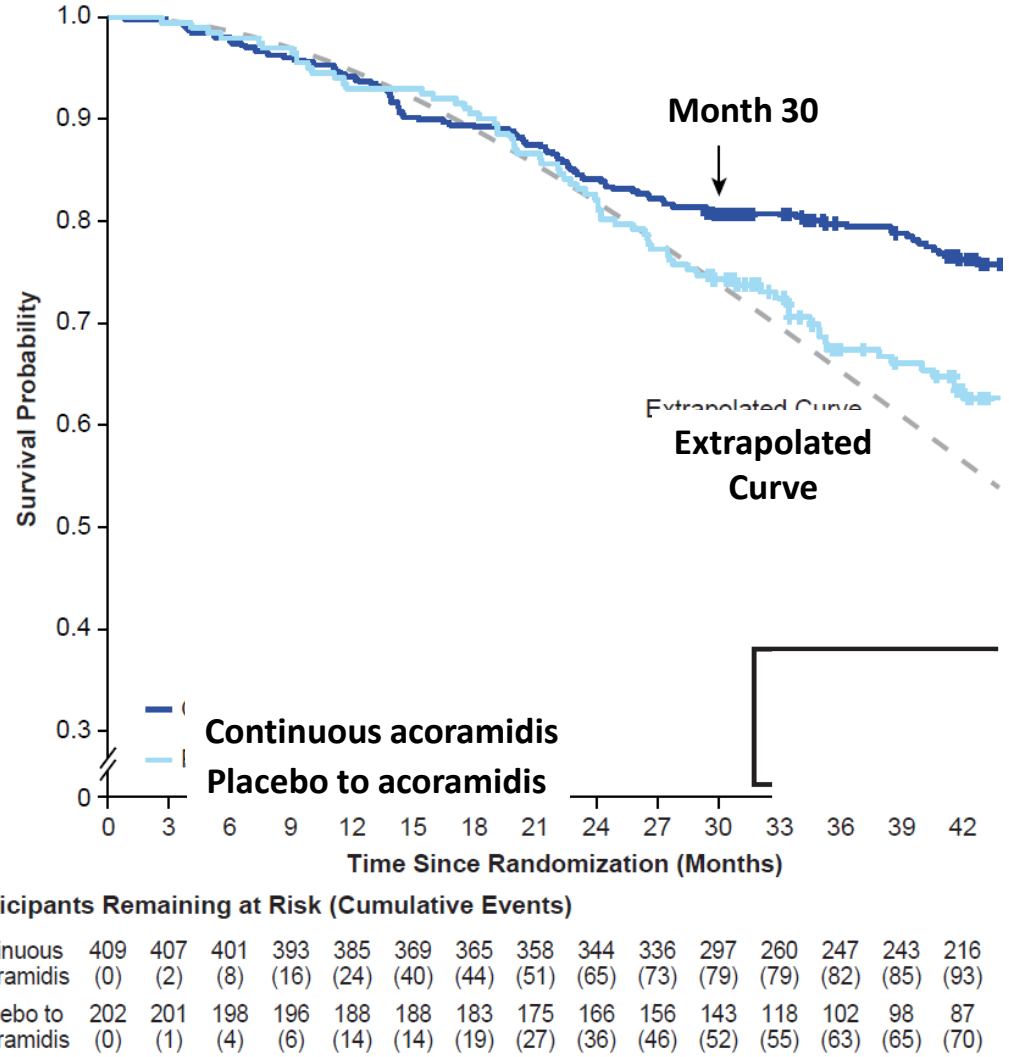
ATTR-CM, transthyretin amyloidosis cardiomyopathy; ATTRwt-CM, transthyretin amyloidosis wild-type cardiomyopathy; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; SD, standard deviation; TTR, transthyretin.

NO NEW SAFETY SIGNALS OF POTENTIAL CLINICAL CONCERN WERE IDENTIFIED THROUGH MONTH 42

Participants with adverse events, n (%)	Ongoing OLE[a–c] OLE start to Month 42 Continuous acoramidis (n = 263)	ATTRibute-CM Study[d] from baseline to Month 30 Acoramidis (n = 421)
Any TEAE	229 (87.1)	413 (98.1)
TEAEs leading to study drug discontinuation	4 (1.5)	39 (9.3)
Any treatment-related TEAE	3 (1.1)	50 (11.9)
Treatment-related serious TEAEs	0 (0.0)	2 (0.5)
Serious TEAEs	88 (33.5)	230 (54.6)
Severe TEAEs	59 (22.4)	157 (37.3)

[a]An AE is considered as an open-label acoramidis TEAE if the AE is not present before the first dose of open-label acoramidis or if it is present but increases in severity during the open-label acoramidis treatment-emergent period. All AEs reported on the "Adverse Events" or "CV Hospitalizations and Events of Clinical Interest" eCRF are included in the analysis. SAE meets seriousness criteria. [b]Relationship to the study drug or severity as assessed by the investigator. [c]Data reflects TEAEs reported in the OLE from start of OLE through M42 (M12 of OLE). [d]Data reflects treatment emergent adverse events in ATTRibute-CM through M30 for participants randomized to acoramidis group. AE, adverse event; CV, cardiovascular; eCRF, electronic case report form; M, month; OLE, open-label extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

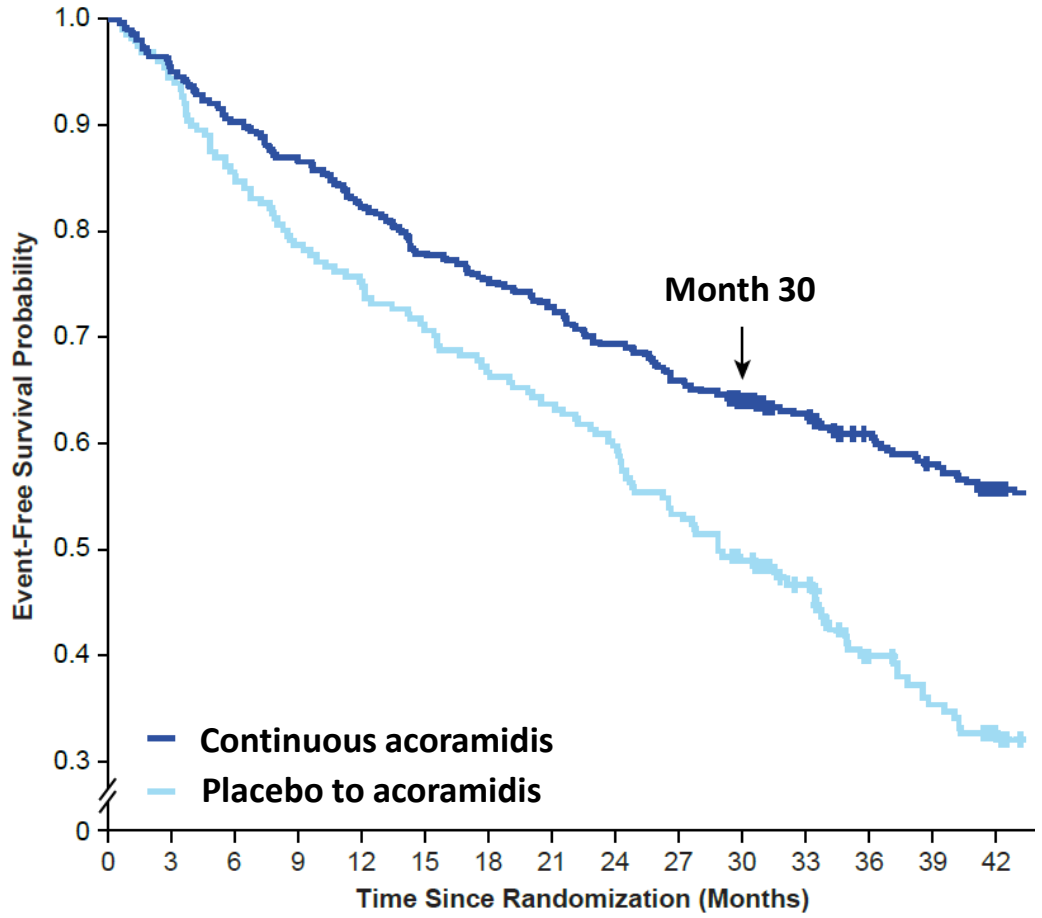
CONTINUOUS ACORAMIDIS REDUCED THE RISK OF ACM AT MONTH 42 VS PLACEBO TO ACORAMIDIS



	Continuous acoramidis (n = 409)	Placebo to acoramidis (n = 202)
Participants with ACM, n (%)	94[a] (23.0)	70 (34.7)
Relative risk reduction	33.7%	
Hazard ratio (95% CI)[b]	0.64 (0.47, 0.88)	
***P* value**	0.0059	

The extrapolated survival curve shows the expected results if participants had continued receiving placebo. Data are for the full analysis set, which included the mITT population in the parent ATTRibute-CM study, defined as all the participants who had undergone randomization, received at least one dose of acoramidis or placebo, and had at least one efficacy evaluation after baseline; participants with Stage 4 chronic kidney disease (eGFR, < 30 mL/min/1.73 m^2) were excluded. [a]One ACM event occurred after M42, but was included in the M42 data cut. [b]Stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate and was stratified by the ATTRibute-CM randomization stratification factors of genotype, NT-proBNP level and eGFR. ACM, all-cause mortality; CI, confidence interval; eGFR, estimated glomerular filtration rate; mITT, modified intention to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

CONTINUOUS ACORAMIDIS REDUCED THE RISK OF ACM OR FIRST CVH AT MONTH 42 VS PLACEBO TO ACORAMIDIS



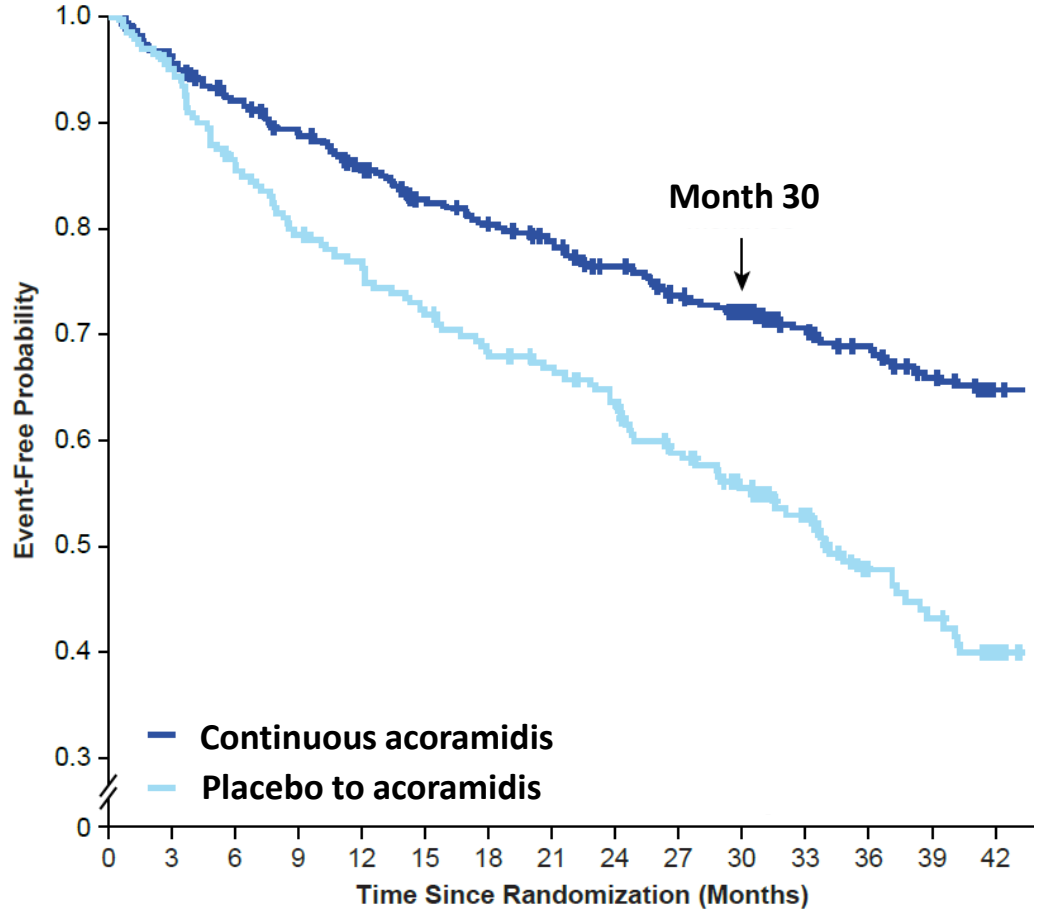
Participants Remaining at Risk (Cumulative Events)

Continuous acoramidis	409 (0)	389 (20)	370 (39)	355 (54)	337 (72)	319 (90)	308 (101)	298 (111)	284 (125)	270 (139)	233 (147)	203 (151)	189 (157)	179 (166)	155 (173)
Placebo to acoramidis	202 (0)	191 (11)	172 (30)	159 (43)	152 (50)	143 (59)	135 (67)	129 (73)	121 (81)	108 (94)	97 (103)	80 (107)	62 (118)	54 (125)	45 (130)

	Continuous acoramidis (n = 409)	Placebo to acoramidis (n = 202)
Participants with ACM or first CVH, n (%)	174[a] (42.5)	130 (64.4)
Relative risk reduction	33.9%	
Hazard ratio (95% CI)[a]	0.57 (0.46, 0. 72)	
***P* value**	< 0.0001	

Data are for the full analysis set. [a]One ACM event occurred after M42 but was included in the M42 data cut. [b]Stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate and was stratified by the ATTRibute-CM randomization stratification factors of genotype, NT-proBNP level and eGFR. ACM, all-cause mortality; CI, confidence interval; eGFR, estimated glomerular filtration rate; mITT, modified intention to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

CONTINUOUS ACORAMIDIS REDUCED THE RISK OF FIRST CVH AT MONTH 42 VS PLACEBO TO ACORAMIDIS



Participants Remaining at Risk (Cumulative Events)

Continuous acoramidis	409 (0)	389 (18)	370 (32)	355 (44)	337 (58)	319 (69)	308 (78)	298 (84)	284 (93)	270 (103)	233 (109)	200 (113)	189 (118)	177 (126)	152 (129)
Placebo to acoramidis	202 (0)	191 (10)	172 (28)	159 (41)	152 (47)	143 (56)	135 (63)	129 (66)	121 (72)	108 (81)	97 (87)	78 (91)	61 (98)	55 (104)	46 (108)

	Continuous acoramidis (n = 409)	Placebo to acoramidis (n = 202)
Participants with CVH alone, n (%)	129 (31.5)	108 (53.5)
Relative risk reduction	41.0%	
Hazard ratio (95% CI)[a]	0.53 (0.41, 0.69)	
***P* value**	< 0.0001	

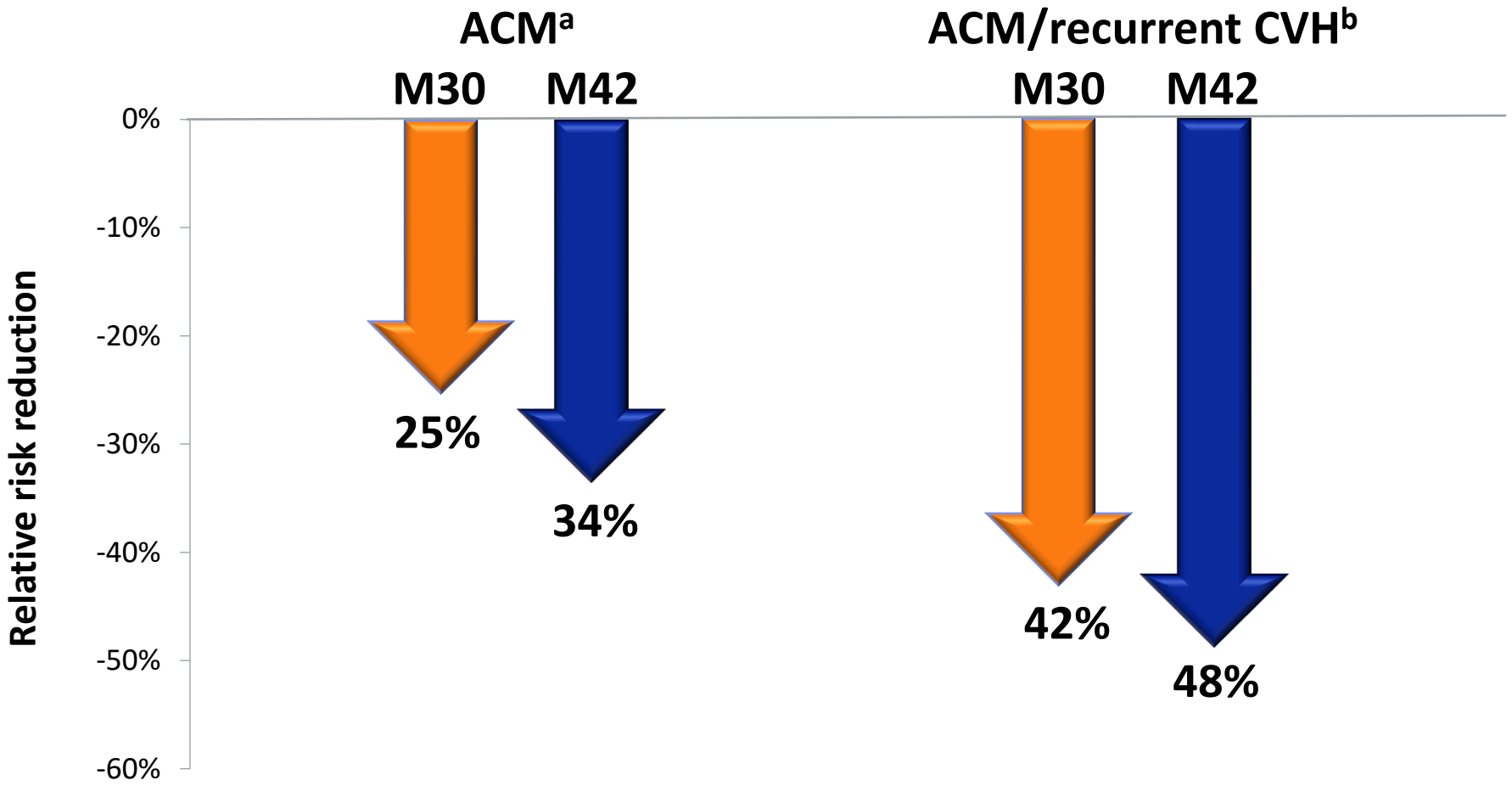
Data are for the full analysis set. [a]Stratified Cox proportional hazards model that included treatment group as an explanatory factor and baseline 6MWD as a covariate and was stratified by the ATTRibute-CM randomization stratification factors of genotype, NT-proBNP level and eGFR. ACM, all-cause mortality; CI, confidence interval; eGFR, estimated glomerular filtration rate; mITT, modified intention to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

CONTINUOUS ACORAMIDIS REDUCED THE RISK OF ACM OR RECURRENT CVH THROUGH MONTH 36 AND MONTH 42 VS PLACEBO TO ACORAMIDIS

	Outcome through Month 36 in the OLE		Outcome through Month 42 in the OLE	
Number of participants with ACM or recurrent CVH events	**Continuous acoramidis n = 409**	**Placebo to acoramidis n = 202**	**Continuous acoramidis n = 409**	**Placebo to acoramidis n = 202**
Participants with ACM or recurrent CVH, n (%)	157 (38.4)	118 (58.4)	174 (42.5)	130 (64.4)
Participants with ACM, n (%)	82 (20.0)	63 (31.2)	94 (23.0)	70 (34.7)
Participants with CVH, n (%)	118 (28.9)	98 (48.5)	129 (31.5)	108 (53.5)
Relative risk reduction[a]	**46%**		**48%**	
Relative risk ratio[b] (95% CI)	0.54 (0.40, 0.73)		0.52 (0.39, 0.68)	
***P* value**	< 0.0001		< 0.0001	

Data are for the full analysis set. [a]Relative Risk Reduction is calculated by (1−relative risk ratio from the negative binomial regression analysis) x 100%. [b]Analyzed by the negative binomial regression model with treatment group, randomization stratification factors of genotype, NT-proBNP level and eGFR level, and the offset term based on the logarithm of the follow-up duration in years. ACM, all-cause mortality; CI, confidence interval; CVH, cardiovascular-related hospitalization; eGFR, estimated glomerular filtration rate; mITT, modified intention to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

RELATIVE RISK REDUCTION OF ACORAMIDIS ON CLINICAL OUTCOMES AT MONTH 30 IS SUSTAINED THROUGH MONTH 42



OLE study limitations: lack of a true control treatment arm, and the exclusion of participants who elected not to enroll in the OLE (most commonly because of a desire to receive tafamidis)

[a]Relative risk reduction based on percent of participants with ACM event at M30 and M42. [b]Relative risk reduction is calculated by (1−relative risk ratio from the negative binomial regression analysis) x 100%.
ACM, all-cause mortality; CVH, cardiovascular-related hospitalization; M, month; OLE, open-label extension.

CONCLUSIONS

Patients who received continuous acoramidis treatment for 42 months had significantly reduced risks of ACM, first CVH, ACM or first CVH, and ACM or recurrent CVH events compared with those who were randomized to receive placebo in ATTRibute-CM

No new clinically important safety issues were identified in this long-term evaluation of acoramidis treatment in up to 42 months

Continuous acoramidis efficacy data, up to Month 42, underscore the critical importance of early diagnosis and prompt initiation of treatment to improve outcomes in ATTR-CM

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

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LONG-TERM EFFICACY AND SAFETY OF ACORAMIDIS IN ATTR-CM: INITIAL REPORT FROM THE OPEN-LABEL EXTENSION OF THE ATTRIBUTE-CM TRIAL

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