Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

Results of the ATTRibute-CM Trial

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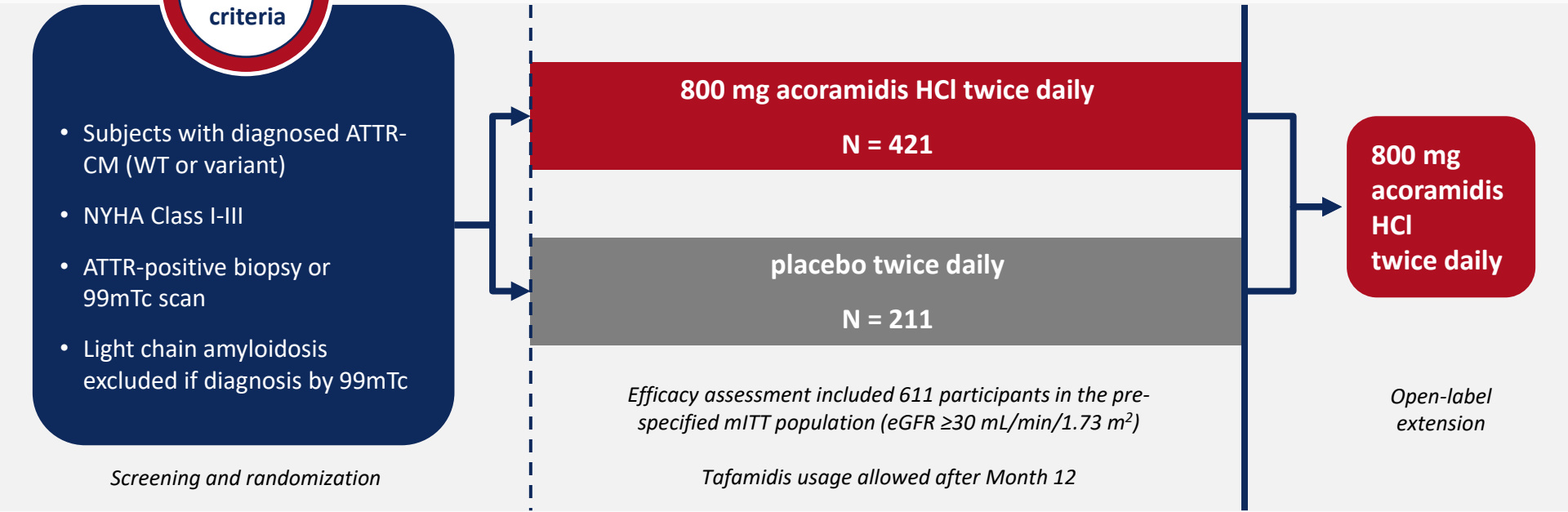
Disclosures

Advisor/consultant for BridgeBio, Alnylam, Ionis, AstraZeneca, Intellia, Pfizer, ATTRalus, Lycia

Acoramidis is an investigational molecule. The safety and efficacy have not been fully evaluated by regulatory authorities.

ATTRibute-CM: Study Design

30-month primary endpoint:
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD



6MWD = Six-minute walk distance; NYHA = New York heart association; 99mTc = Technetium labeled pyrophosphate (PYP) or bisphosphonate (e.g., DPD); mITT = Modified intent-to-treat. eGFR = Estimated glomerular filtration rate. ClinicalTrials.gov identifier: NCT03860935.

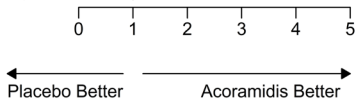
ATTRibute-CM: Baseline Demographic Characteristics

Characteristic	Acoramidis (N=421)	Placebo (N=211)
Age (years), mean (SD)	77.4 (6.5)	77.1 (6.8)
Male sex, n (%)	384 (91.2)	186 (88.2)
ATTRwt-CM, n(%)	380 (90.3)	191 (90.5)
NT-proBNP (pg/mL), median (IQR)	2326 (1332, 4019)	2306 (1128, 3754)
eGFR (mL/min/1.73m^2), mean (SD)	60.9 (18.2)	61.0 (18.7)
TTR (mg/dL), mean (SD)	23.2 (5.6)	23.6 (6.1)
KCCQ-OS, mean (SD)	71.5 (19.4)	70.3 (20.5)
6MWD (m), mean (SD)	361.2 (103.7)	348.4 (93.6)
Concomitant tafamidis use, n (%)*	61 (14.5)	46 (21.8)

ATTRwt-CM = Transthyretin amyloidosis wild-type cardiomyopathy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; IQR = interquartile range; TTR = transthyretin; KCCQ-OS = Kansas City cardiomyopathy questionnaire overall summary score.
*Tafamidis usage allowed after Month 12.

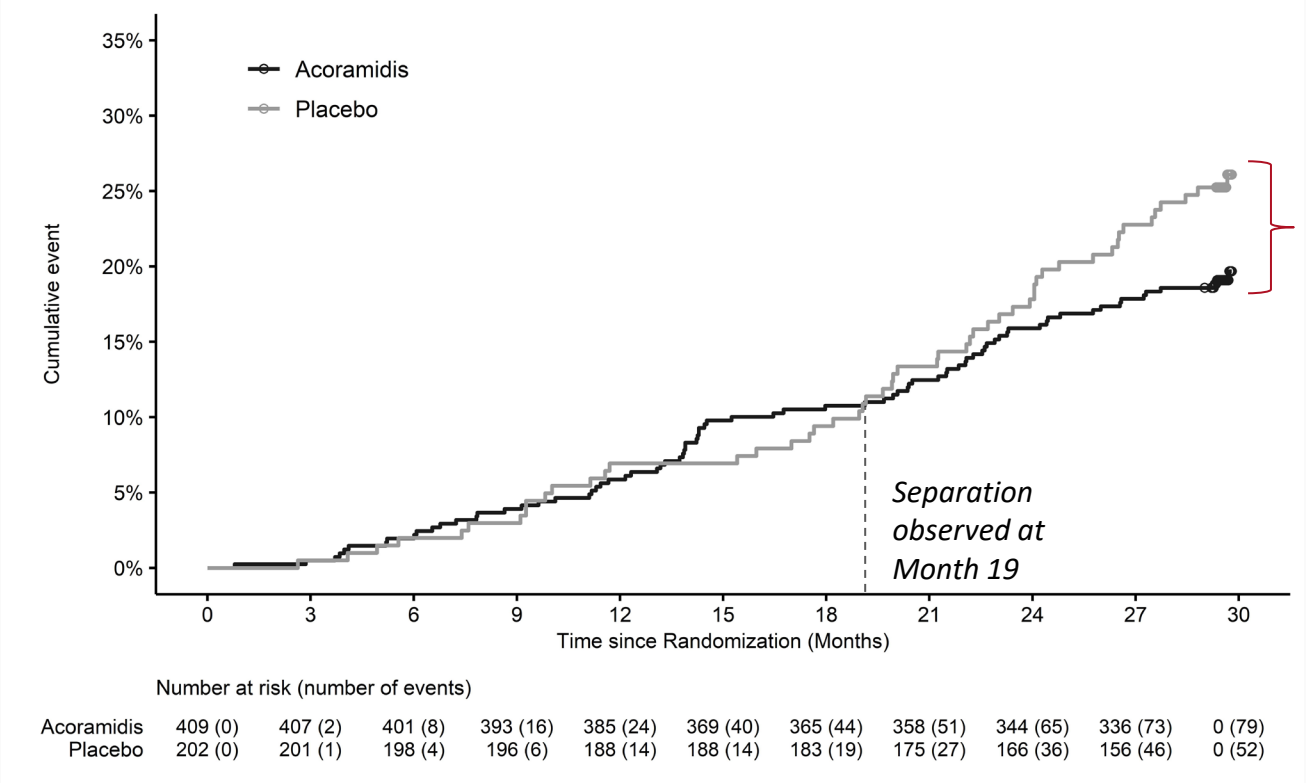
ATTRibute-CM: Primary Outcome Overall and by Subgroups

Subgroup	No. of Patients	Win Ratio [95% CI]	FS test P-value
Overall	611(100.0)	1.772 [1.417, 2.217]	<0.0001
ATTR-CM Genotype			
ATTRm-CM	59(9.7)	2.529 [1.303, 4.911]	0.0061
ATTRwt-CM	552(90.3)	1.756 [1.396, 2.208]	<0.0001
NT-proBNP (pg/mL)			
<= 3000	401(65.6)	1.787 [1.373, 2.325]	<0.0001
> 3000	210(34.4)	1.678 [1.160, 2.426]	0.0060
eGFR (mL/min/1.73m2)			
< 45	94(15.4)	1.410 [0.849, 2.341]	0.1841
>= 45	517(84.6)	1.797 [1.452, 2.226]	<0.0001
Age (years)			
< 78	299(48.9)	2.052 [1.489, 2.829]	<0.0001
>= 78	312(51.1)	1.499 [1.098, 2.045]	0.0107
NYHA Class			
I, II	512(83.8)	1.892 [1.479, 2.419]	<0.0001
III	99(16.2)	1.150 [0.652, 2.030]	0.6292



FS = Finkelstein-Schoenfeld; CI = Confidence interval.

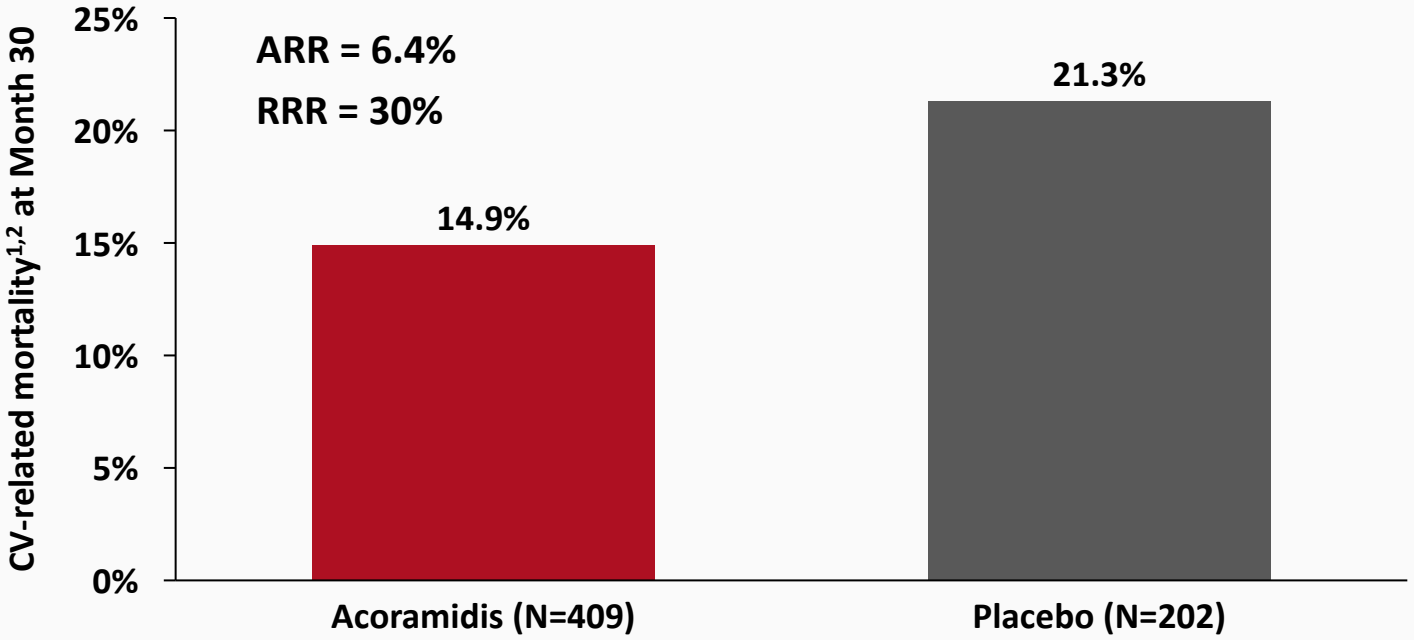
ATTRibute-CM: All-Cause Mortality



ARR = Absolute risk reduction; RRR = Relative risk reduction.

All-cause mortality includes heart transplant, implantation of cardiac mechanical assist device, and all-cause death.

ATTRibute-CM: Cardiovascular-Related Mortality



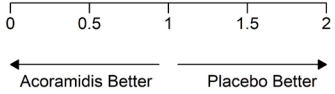
CV-related: Cardiovascular-related.

[1]Heart transplant and implantation of cardiac mechanical assistance device (CMAD) were treated as death for this analysis. N =1 heart transplant & N = 1 CMAD implantation in placebo group.

[2]CV-related mortality includes all adjudicated CV-related and undetermined cause of death.

ATTRibute-CM: Frequency of CVH; P<0.0001 on overall analysis

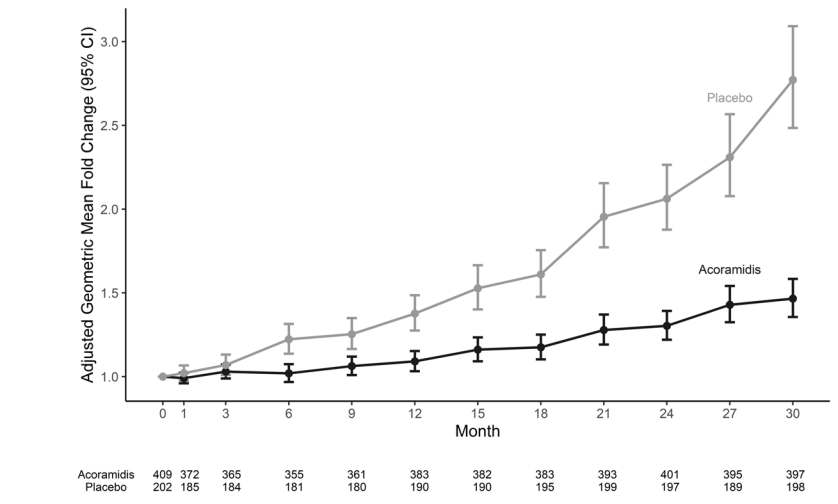
Subgroup	No. of Patients	Relative Risk [95% CI]
Overall	611(100.0)	0.496 [0.355, 0.695]
ATTR-CM Genotype		
ATTRm-CM	59(9.7)	0.377 [0.139, 1.027]
ATTRwt-CM	552(90.3)	0.514 [0.360, 0.734]
NT-proBNP (pg/mL)		
<= 3000	401(65.6)	0.456 [0.299, 0.695]
> 3000	210(34.4)	0.576 [0.330, 1.003]
eGFR (mL/min/1.73m2)		
< 45	94(15.4)	0.594 [0.250, 1.415]
>= 45	517(84.6)	0.481 [0.334, 0.692]
Age (years)		
< 78	299(48.9)	0.437 [0.275, 0.696]
>= 78	312(51.1)	0.576 [0.353, 0.940]
NYHA Class		
I, II	512(83.8)	0.447 [0.310, 0.645]
III	99(16.2)	0.721 [0.313, 1.660]



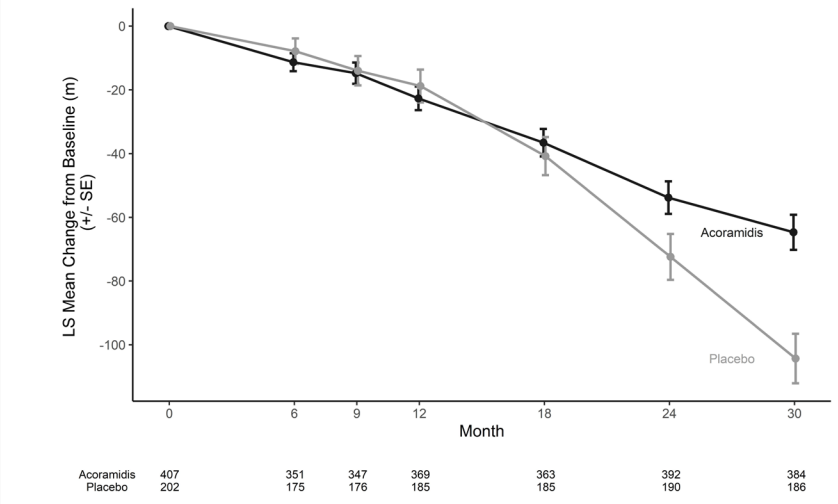
Negative binomial regression with treatment group, stratification factors, and subgroup of interest was used to analyze the cumulative frequency of adjudicated CV-related hospitalization.

ATTRibute-CM: Change from Baseline in NT-proBNP & 6MWD

Change from Baseline in NT-proBNP[1]



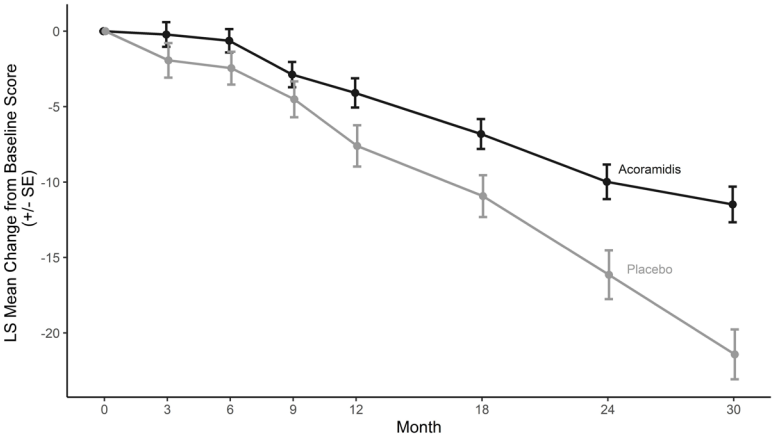
Change from Baseline in 6MWD[1]



[1]Analyzed using mixed effects model with repeated measures. Missing measurements due to early discontinuation imputed using the Jump to Reference method. Missing measurements due to death performed by sampling with replacement from bottom 5% of observed values.

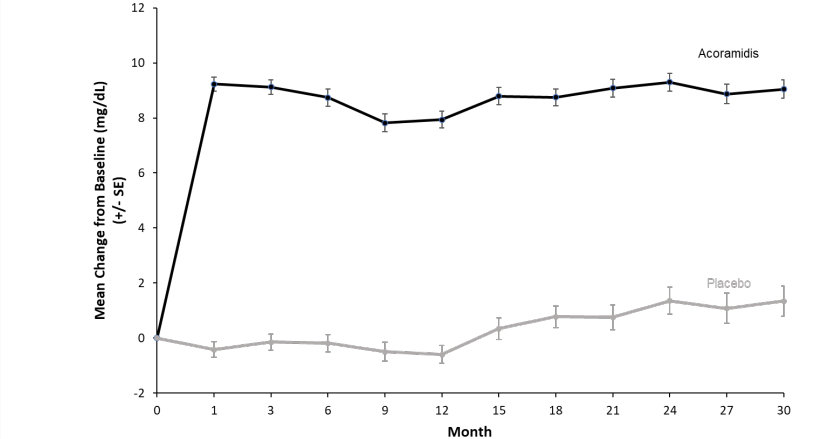
ATTRibute-CM: Change from Baseline in KCCQ-OS & Serum TTR

Change from Baseline in KCCQ-OS[1]



Acoramidis	408	263	389	390	397	404	407	405
Placebo	202	134	192	194	196	199	201	201

Change from Baseline in Serum TTR[2]

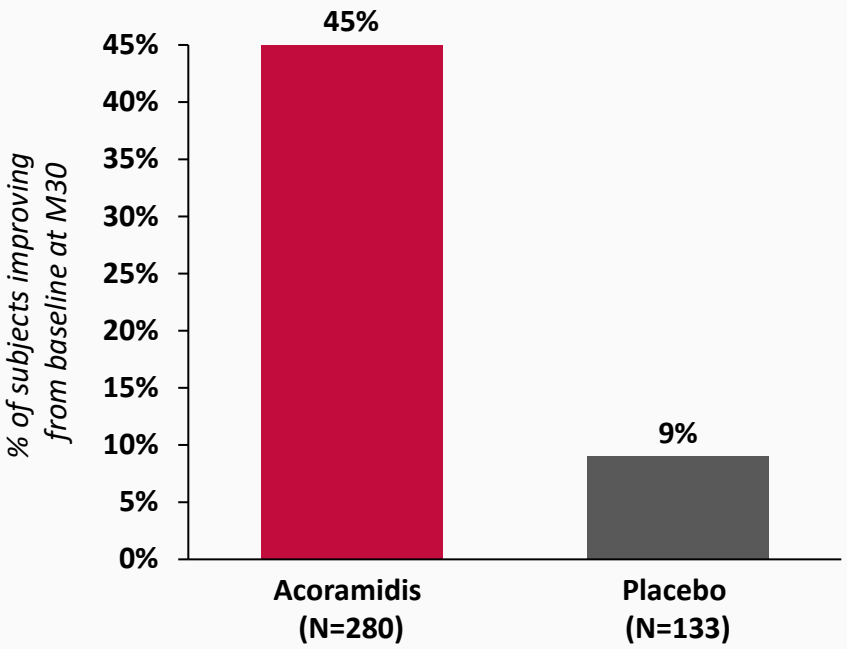


Acoramidis	406	363	348	324	319	328	307	300	294	297	280	283
Placebo	199	178	175	165	162	168	160	160	154	142	128	135

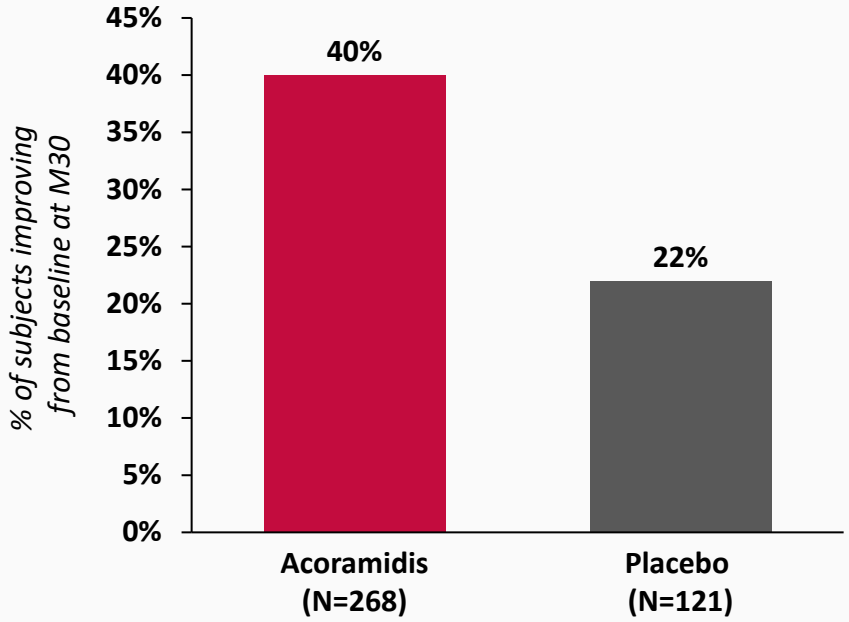
[1]Analyzed using mixed effects model with repeated measures. Missing measurements due to early discontinuation imputed using the Jump to Reference method. Missing measurements due to death performed by sampling with replacement from bottom 5% of observed values. [2]Observed measurements without any imputation. No adjustment was made for early discontinuation for any reason, including death.

ATTRibute-CM: Improvements in Disease Measures

Improvement from baseline in NT-proBNP



Improvement from baseline in 6MWD



mITT population. Improvement is defined as <0 pg/mL change from baseline to month 30 for NT-proBNP; >0 meter change from baseline to month 30 for 6MWD. In both cases, among subjects with both baseline and month 30 values.

ATTRibute-CM: Patient Safety

Subjects with one or more event(s)	Acoramidis N=421 N (%)	Placebo N=211 N (%)
Any treatment-emergent adverse events (TEAEs)	413 (98.1%)	206 (97.6%)
TEAE with fatal outcome	60 (14.3%)	36 (17.1%)
TEAE leading to hospitalization	212 (50.4%)	128 (60.7%)
TEAE leading to study drug discontinuation	39 (9.3%)	18 (8.5%)
Any treatment-emergent serious adverse events (SAEs)	230 (54.6%)	137 (64.9%)
Treatment-emergent SAEs leading to study drug discontinuation	21 (5.0%)	15 (7.1%)
Severe TEAEs[1]	157 (37.3%)	96 (45.5%)

Acoramidis was generally well-tolerated with no findings of potential clinical concern

All Adverse Events (AEs) occurring during the treatment period are considered treatment-emergent adverse events (TEAEs). Serious Adverse Event (SAE) meets seriousness criteria.
[1]Severity as assessed by the investigator.

ATTRibute-CM: Conclusions

- **Primary endpoint analysis (Finkelstein-Schoenfeld hierarchy of ACM, CVH, NT-proBNP, 6MWD) highly statistically significant**
  - Win ratio 1.8; p<0.0001; 58% of win ratio ties broken by ACM + CVH
- **Consistent treatment effect across secondary endpoints**
  - Better preservation of functional capacity (6MWD) and QoL (KCCQ-OS)
  - Reduced progressive increase in NT-proBNP; 45% of patients improved
- **81% survival rate on acoramidis approaches survival rate in age-matched US database (~85%)[1,2]**
- **0.29 mean annual CVH frequency on acoramidis approaches annual hospitalization rate observed in broader US Medicare population (~0.26)[3]**
- **Reassuring safety profile**

[1]ssa.gov. [2]Miller et al., Am J Card 2021 [3]US Department of Health & Human Services, Jan 2018.

ATTRibute-CM: Acknowledgements

- Patients, caregivers
- Investigators, research staff
- Steering Committee, Data Monitoring Committee, Clinical Events Committee, Data Reporting Center
- Patient advocacy organizations
- BridgeBio scientists and supporting employees