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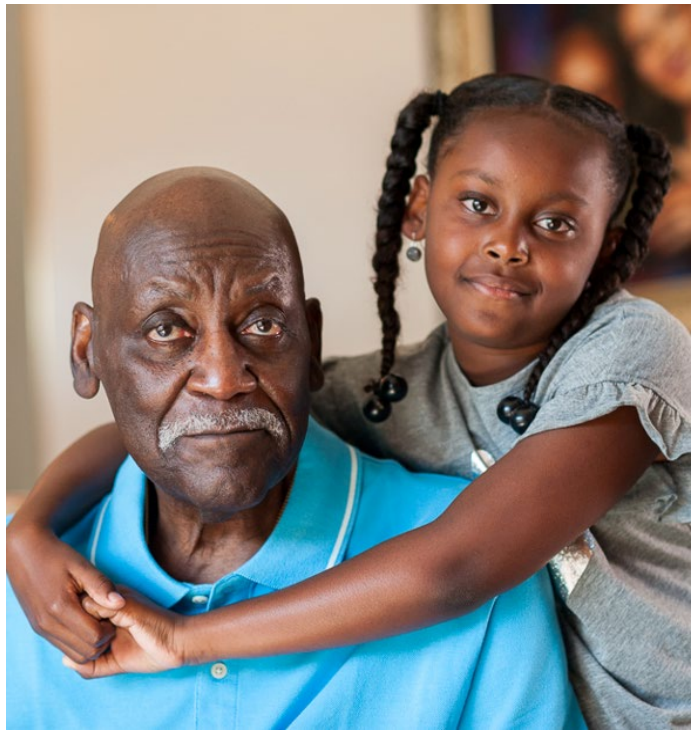
Acoramidis Improves Clinical Outcomes in ATTR-CM: Additional Data from ATTRibute-CM Phase 3 Study

November 12, 2023



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Discussion topics

1. Molecular hypothesis
2. Additional clinical outcomes data from ATTRibute-CM
3. Context for clinical findings
4. Next steps
5. Q&A session

Acoramidis was designed to achieve maximal stabilization and preserve native TTR

Design Objectives	Rationale
1 **Maximize TTR stabilization/minimize toxic monomer**	• Strong genotype/phenotype correlation between TTR instability and disease severity[1] • Dose-dependent improvements in both TTR stabilization and clinical outcomes demonstrated by tafamidis in ATTR-CM[2] • Extent of TTR stabilization or knockdown associated with degree of clinical benefit in ATTR-PN[3-6]
2 **Preserve circulating native TTR**	• TTR has been highly conserved throughout evolution[7] • TTR is an abundant plasma protein with relatively rapid turnover requiring sustained metabolic energy expenditure

We plan to enter the ATTR-CM market with acoramidis, a next generation, potent TTR stabilizer

TTR = Transthyretin; ATTR-CM = TTR amyloid cardiomyopathy.

[1]Hammarstrom, P et al., PNAS. 2002;99:16427-16432. [2]Damy, T., et al., Eur J Heart Fail. 2021;23(2):277-285. [3]Coelho, T. et al., Neurology. 2012;79:785–792. [4]Berk, JL et al , JAMA. 2013;310:2658-2667. [5]Adams, DA. et al., N Engl J Med. 2018;379:11-21. [6]Benson, M.D., et al., N Engl J Med. 2018;379:22-31. [7]Richardson SJ, et al. Front Endocrinol. 2015;5:1-9.

Acoramidis is a next generation stabilizer that employs multiple strategies to maximize potency

Disease mechanism

Native TTR circulates in blood as a tetramer

~130 known destabilizing mutations

Protective T119M mutation

Dissociation into monomers initiates pathogenesis

Monomers aggregate, causing disease

Therapeutic hypothesis

Acoramidis was designed to mimic protective T119M mutation. Acoramidis sees more target (superior free fraction), binds more target (superior kd2), and glues the target together stronger (enthalpic binding mode).[1,2] Phase 3 results confirm differential stabilization via effects on serum TTR.

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

[1]Data on File. [2]Miller, M. et al. J Med Chem. 2018;61:7862-7876.

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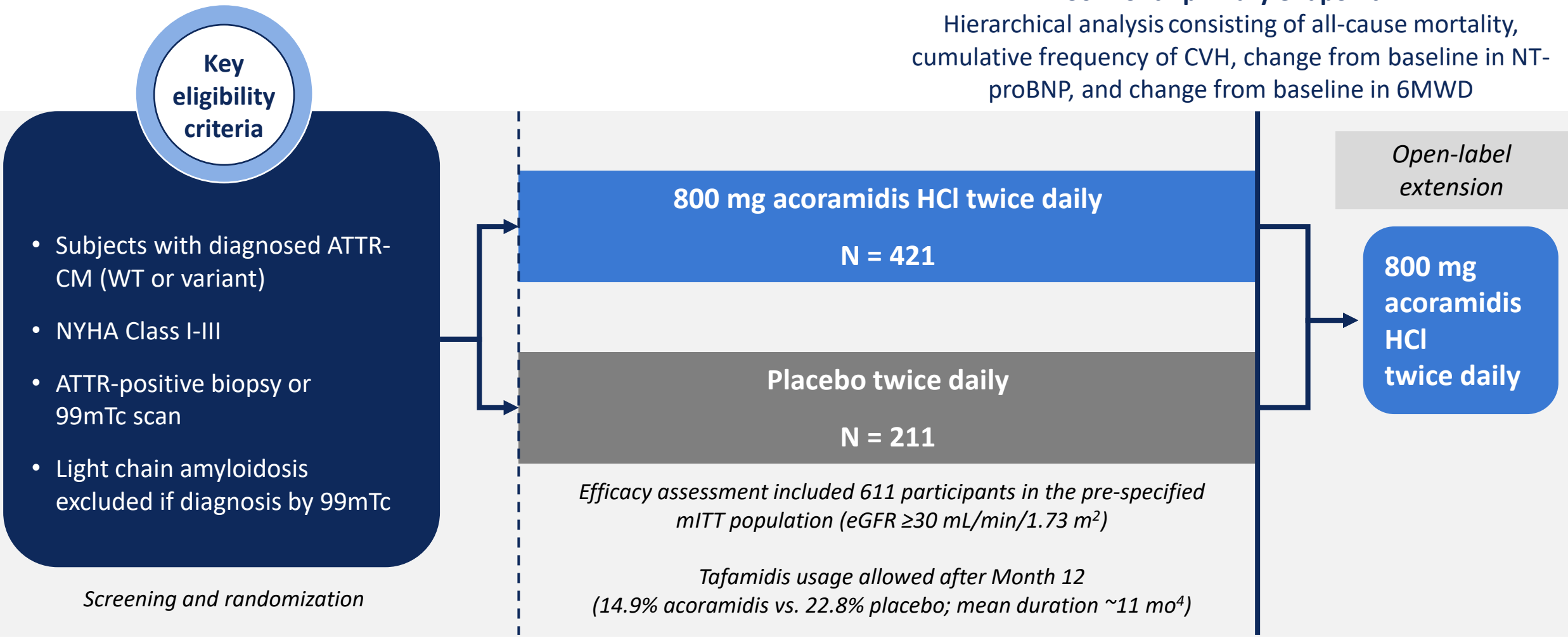
ATTRibute-CM Phase 3 Study Design[1,2]

30-month primary endpoint[3]:
Hierarchical analysis consisting of all-cause mortality, cumulative frequency of CVH, change from baseline in NT-proBNP, and change from baseline in 6MWD



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

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.

[1]ClinicalTrials.gov identifier: NCT03860935. [2]Gillmore JD et al. Circulation. 2019;140(1):14214. Oral poster presented at AHA. [3]Primary analysis assessed using the Finkelstein-Schoenfeld method. [4]In mITT study population.

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) [nl <300]	2326 (1332, 4019)	2306 (1128, 3754)
eGFR (mL/min/1.73m^2), mean (SD)	60.9 (18.2)	61.0 (18.7)
NAC Stage I n(%)	241 (57.2)	120 (56.9)
NAC Stage II n(%)	134 (31.8)	69 (32.7)
NAC Stage III n(%)	46 (10.9)	22 (10.4)
Serum TTR (mg/dL), mean (SD) [nl 20-40]	23.2 (5.6)	23.6 (6.1)
KCCQ-OS, mean (SD) [range 0-100]	71.5 (19.4)	70.3 (20.5)
6MWD (m), mean (SD)	361.2 (103.7)	348.4 (93.6)

ATTRwt-CM = Transthyretin amyloidosis wild-type cardiomyopathy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; IQR = interquartile range; nl: norma levels; NAC = National Amyloidosis Centre; Stage I (NT-proBNP ≤3000 ng/L and eGFR ≥45 ml/min), Stage II (NT-proBNP ≤3000 ng/L and eGFR <45 ml/min or NT-proBNP >3000 ng/L and eGFR ≥45 ml/min), Stage III (NT-proBNP >3000 ng/L and eGFR <45 ml/min); TTR = transthyretin; 6MWD = 6-minute walk distance; KCCQ-OS = Kansas City cardiomyopathy questionnaire overall summary score.

Results Achieved On Primary And Select Secondary Endpoints

Primary endpoint[1]	p-value
Hierarchical analysis consisting of: • All-cause mortality[2] • Cumulative frequency of CVH • Change from baseline in NT-proBNP • Change from baseline in 6MWD	p<0.0001
Win Ratio	1.8

58% of ties broken by first two components of Win Ratio analysis

Select secondary endpoints	p-value
Cumulative frequency of CVH[3]	p<0.0001
Change from baseline in 6MWD[4]	p<0.0001
Change from baseline in KCCQ-OS[4]	p<0.0001
Change from baseline in serum TTR[4]	p<0.0001
Change from baseline in NT-proBNP[5]	p<0.0001
All-cause mortality[2,6]	p=0.057
CV-related mortality[2,7]	p=0.037

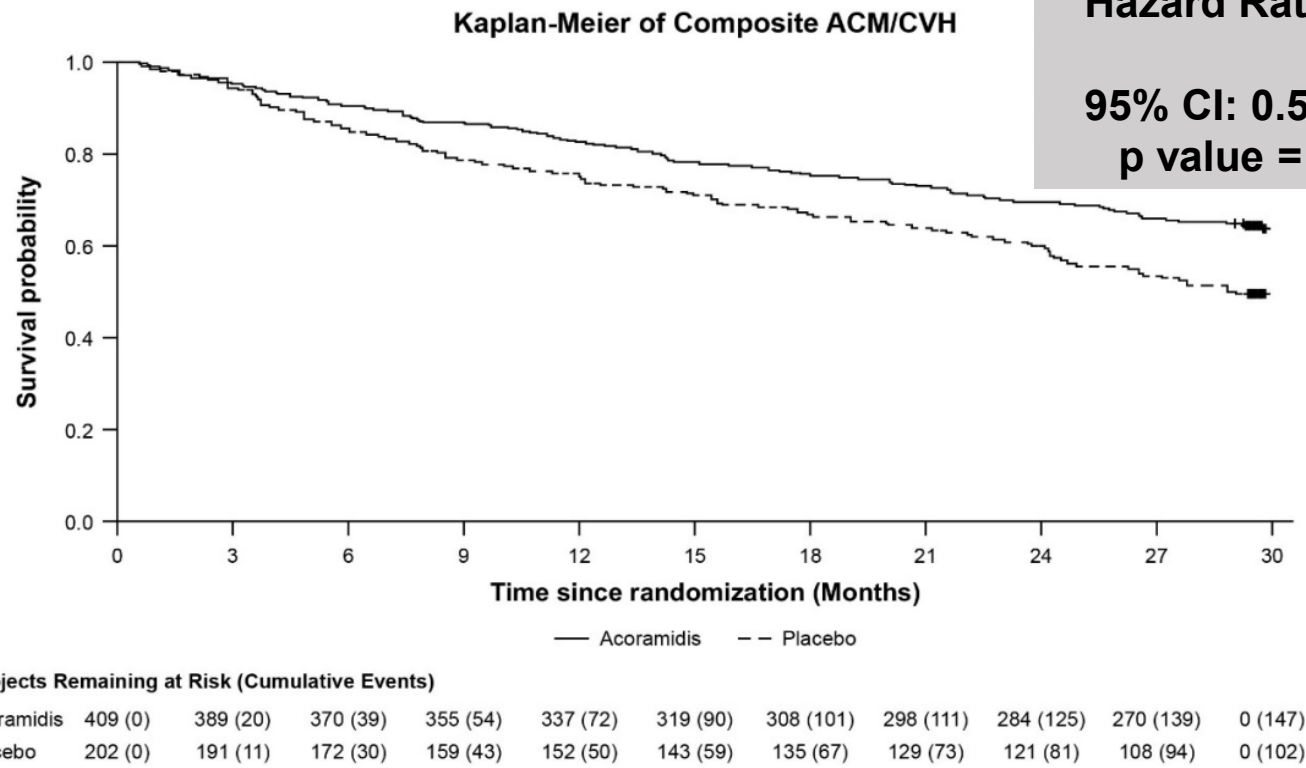
25% RRR in ACM[2,8]

30% RRR in CVM[2,9]

[1]Primary analysis assessed using the Finkelstein-Schoenfeld method. [2]Heart transplant and implantation of cardiac mechanical assistance device were treated as death for this analysis. [3]Negative binomial regression model .[4]Least squares mean difference change from baseline at 30 months; [5]Ratio of adjusted geometric mean fold change from baseline at 30 months. [6]Assessed by Cochran-Mantel-Haenszel test; p=0.15 as assessed by Cox Proportional Hazard Model. [7]Assessed by Cochran-Mantel-Haenszel test; p=0.089 as assessed by Cox Proportional Hazard Model. [8]19.3% for acoramidis and 25.7% for placebo. [9]14.9% in acoramidis vs. 21.3% for placebo. CV-related mortality is any all-cause mortality event adjudicated as due to a cardiovascular or undetermined cause.

Composite ACM/CVH: Time-to-First Event & F-S Test

K-M curves separate early, at Month 3, and steadily diverge through Month 30



Subjects Remaining at Risk (Cumulative Events)

Acoramidis	409 (0)	389 (20)	370 (39)	355 (54)	337 (72)	319 (90)	308 (101)	298 (111)	284 (125)	270 (139)	0 (147)
Placebo	202 (0)	191 (11)	172 (30)	159 (43)	152 (50)	143 (59)	135 (67)	129 (73)	121 (81)	108 (94)	0 (102)

Hazard Ratio: 0.645

95% CI: 0.500-0.832
p value = 0.0008

Number Needed to Treat (NNT) to avoid a death or first CVH over 2.5 years

7

2-Component F-S Test (ACM,CVH)

→

Favors acoramidis over placebo

p value = 0.0162

F-S = Finkelstein-Schoenfeld; K-M = Kaplan-Meier; ACM = All-cause mortality; CVH = Cardiovascular-related hospitalization.

Cumulative Frequency Of CV Hospitalizations (CVH):

50% reduction with acoramidis

	Acoramidis (N=409)	Placebo (N=202)
Number of subjects with CVH[1]	109 (26.7%)	86 (42.6%)
Frequency CVH per year (modeled)[2]		
Mean (95% CI)	0.22 (0.18-0.28)	0.45 (0.35-0.58)
Relative Risk Ratio (95% CI)	0.496 (0.355-0.695)	
p value	< 0.0001	

NNT to prevent one CV Hospitalization per year

5

[1]Cardiovascular-related hospitalization as positively adjudicated by Clinical Events Committee, includes Events of Clinical Interest. [2]Negative binomial regression model.

No Safety Signals Of Potential Clinical Concern Identified

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%)

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.

Putting Results In Context

- These contemporary data reset clinical expectations in the treatment and management of today's ATTR-CM patients, who are diagnosed earlier and live longer
  - 30-month mortality rate of ATTRibute-CM placebo (25.7%) less than ATTR-ACT tafamidis (29.5%)
- Outcomes in acoramidis treatment population (previously presented at ESC 2023) approach age-matched general population
  - 81% survival rate on acoramidis approaches survival rate in age-matched US database (~85%)[1,2]
  - 0.29 observed mean annual CVH frequency on acoramidis approaches annual hospitalization rate observed in broader US Medicare population (~0.26)[3]
- Time-to-separation demonstrated at 3 months, representing the most rapid clinical benefit on the composite endpoint of all-cause mortality and CV hospitalization outcomes in ATTR-CM to our knowledge
- Early and profound reduction in CVH can have significant impact on public health and reduce overall treatment costs (~$20k for each hospitalization in US[4])
  - CVH has been shown to be a predictor of mortality in general heart failure[5] and in ATTR-CM[6]

[1]ssa.gov. [2]Miller et al., Am J Card 2021 [3]US Department of Health & Human Services, Jan 2018.
[4]Kazi DS et al. Circulation. 2020;141(15):1214-1224. [5]Bello NA et al. Circulation: Heart Failure. 2014;7:590–595. [6]Masri A et al. HFSA 2023 Scientific Sessions

Conclusion: Acoramidis Improves Clinical Outcomes In ATTR-CM

ATTRibute-CM study results demonstrate that acoramidis improves clinical outcomes (All-Cause Mortality/CV Hospitalization) in ATTR-CM patients:

- Primary Endpoint (4-component F-S analysis) showed a significant treatment benefit of acoramidis over placebo, with majority of ties broken by first 2 components (ACM, Frequency of CVH)
- Notable, early separation at 3 months, based on Time-to-First Event Kaplan-Meier Analysis
  - NNT to prevent an event of death or first CVH over 2.5 years: 7
- 2-component (ACM, Frequency of CVH) F-S analysis shows a significant treatment benefit of acoramidis over placebo

Individual Outcome Components:

- 25% relative risk reduction in All-Cause Mortality: Favorable trend
- 50% relative risk reduction in Cumulative Frequency of CVH (NNT to prevent one CVH/year: 5)

ACM = All-Cause Mortality; CVH = Cardiovascular-Related Hospitalization; F-S = Finkelstein-Schoenfeld method.

Discussion topics

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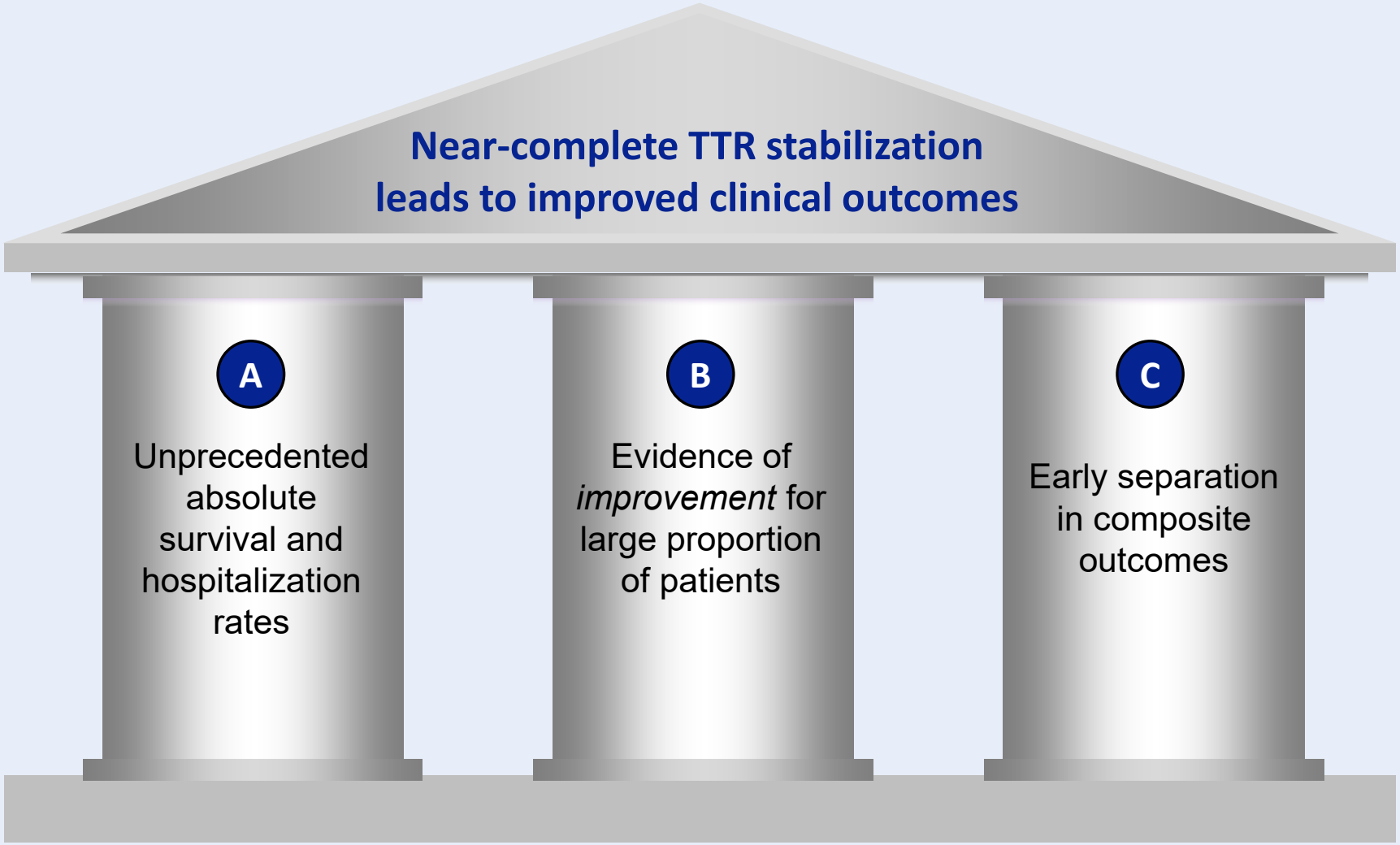
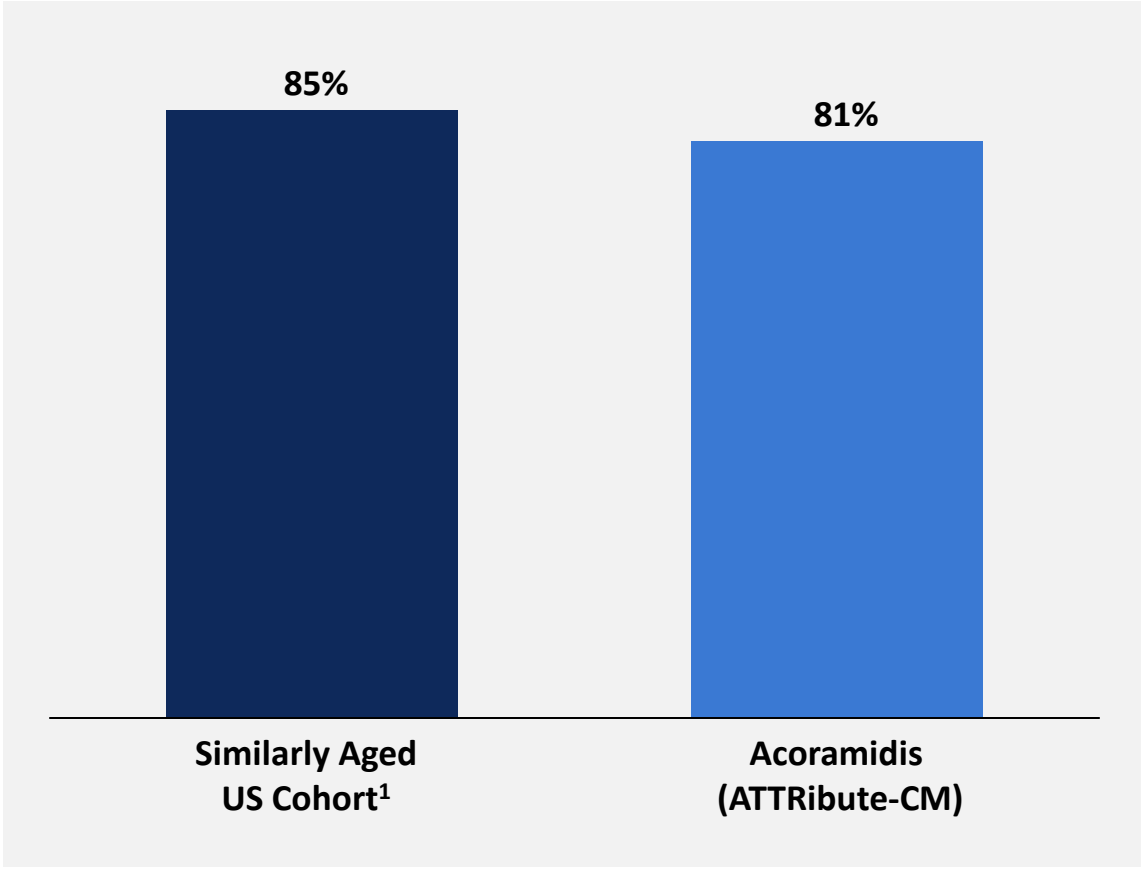
Patients on acoramidis are surviving more and going to the hospital less

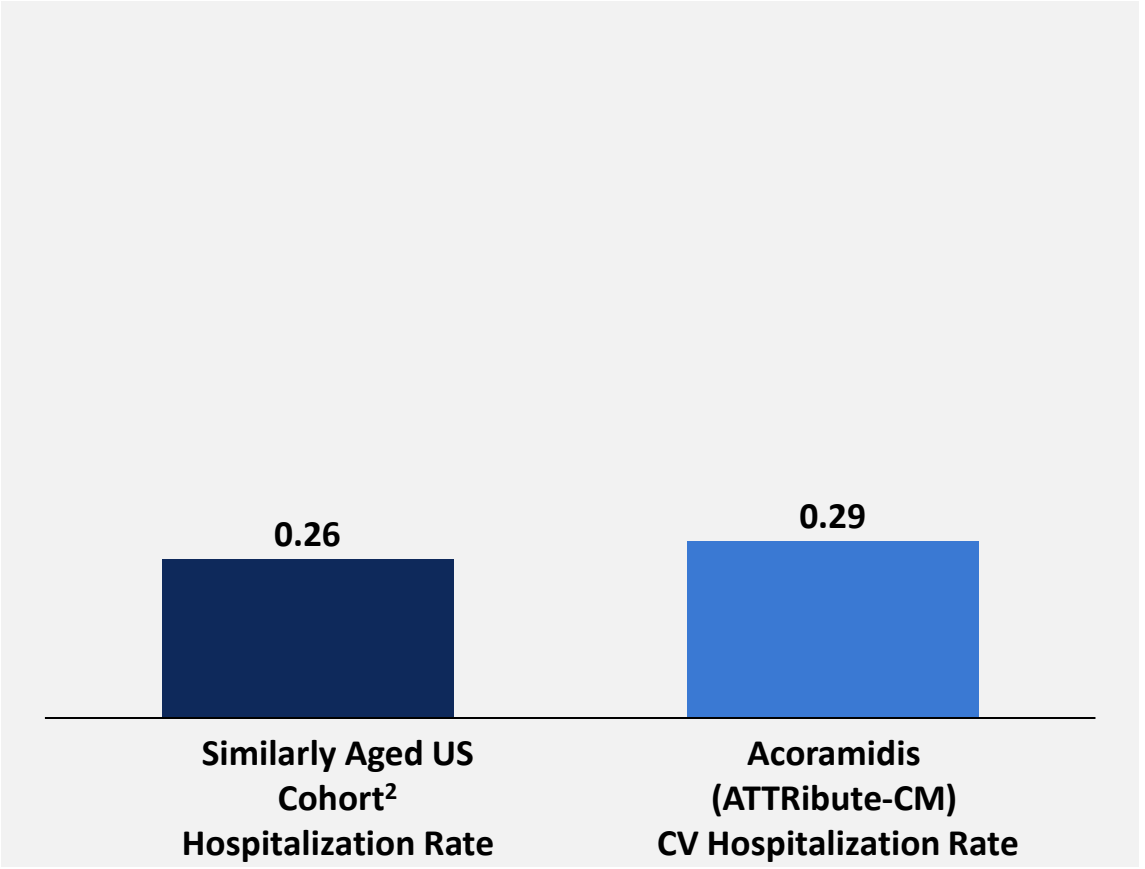


A Observed effect of acoramidis approaches rates of mortality and hospitalization in similarly aged US cohorts

Rate of Survival at Month 30

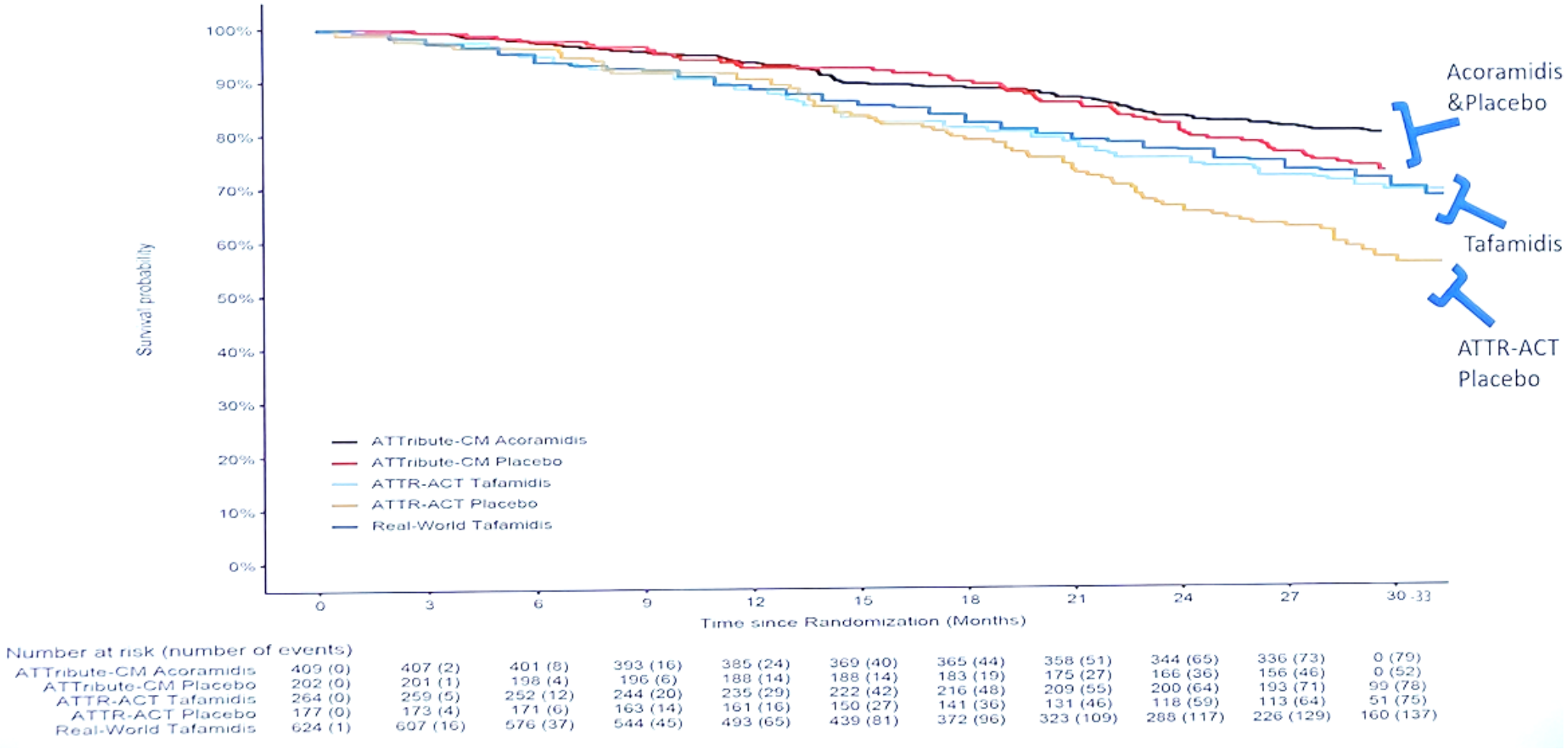


Mean Annual Hospitalization Frequency[3]



Note: Direct cross-study comparisons may suggest misleading similarities or differences. The values shown are directional and do not report robust comparative analysis.
[1]ssa.gov. [2]US Department of Health & Human Services 2018. [3]Natural history reflects US Medicare non-neonatal, non-maternal inpatient stays. ATTRibute-CM and ATTR-ACT data reflect cardiovascular-related hospitalizations.

A Dr. Masri HFSA data: 30-month survival

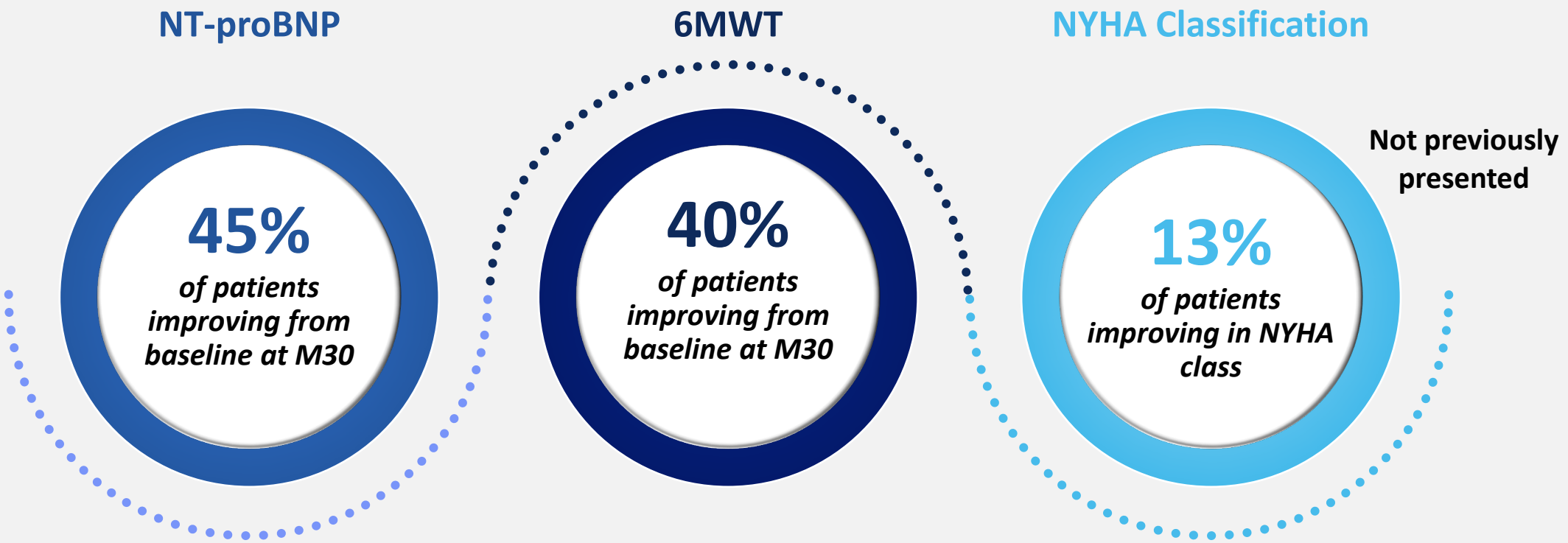


Number at risk (number of events)

ATTribute-CM Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
ATTribute-CM Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)
ATTR-ACT Tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)
ATTR-ACT Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)
Real-World Tafamidis	624 (1)	607 (16)	576 (37)	544 (45)	493 (65)	439 (81)	372 (96)	323 (109)	288 (117)	226 (129)	160 (137)

Source: Masri et al., HFSA 2023 “A Multicenter Study Of Real-world Outcomes Of Tafamidis In Transthyretin Amyloid Cardiomyopathy”.
Note: Direct cross-study comparisons may suggest misleading similarities or differences.

B >40% of mITT participants with data at Month 30 experienced improvement in laboratory and functional measures of disease progression on acoramidis

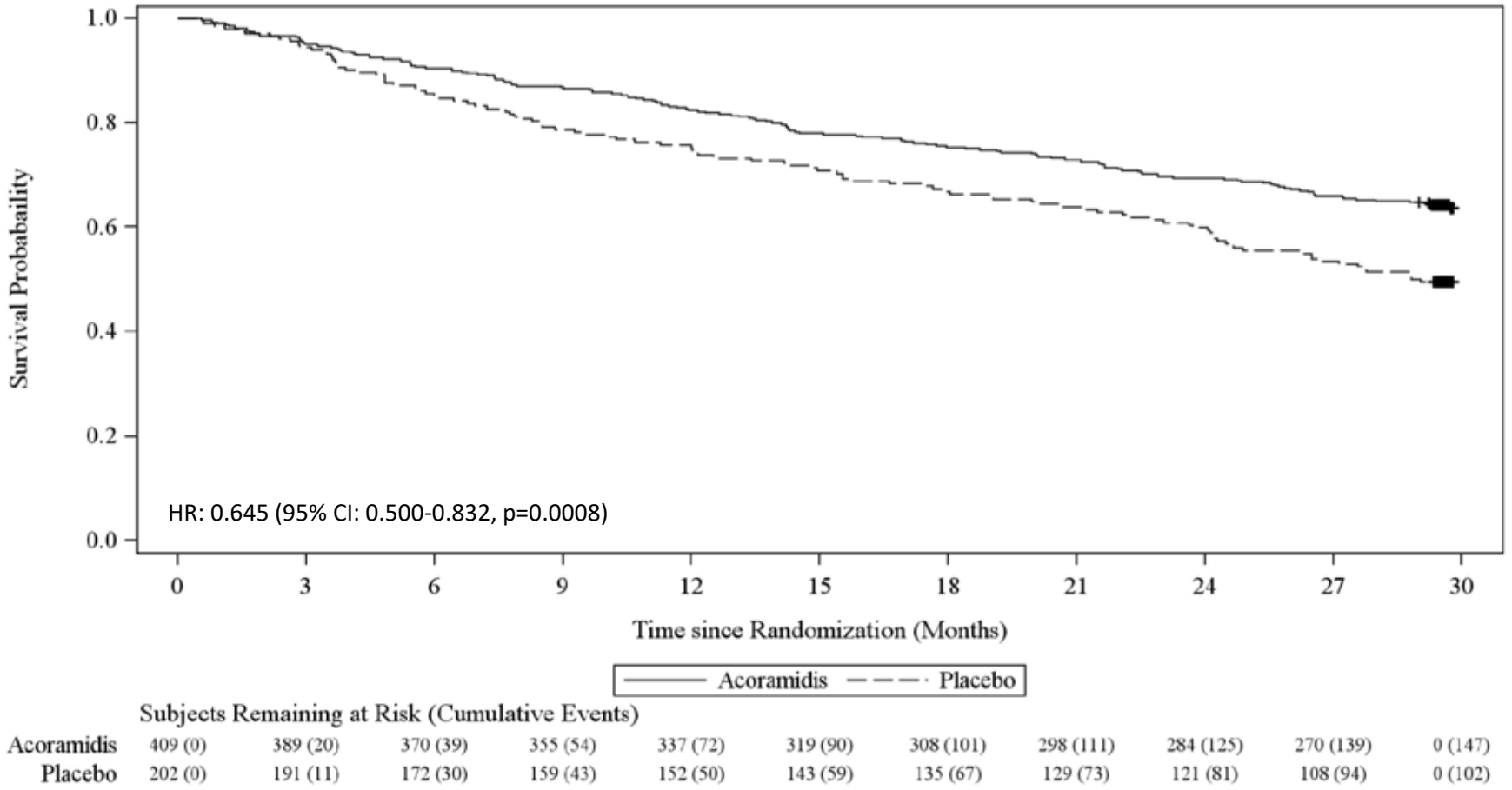


The proportion of patients improving on acoramidis across laboratory and functional measures represent the best observed improvements from prior interventional studies or benchmarks, to the company's knowledge. Even using a conservative imputation method that attributes missing values as unfavorable, the improvements are still the highest observed to the company's knowledge.

Note: Data from ATTRibute-CM Acoramidis study (N=280 for NT-proBNP, N=268 for 6MWT, and N=289). N represents number of patients with data at both baseline and Month 30. ATTRibute-CM data reflects 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; a lower NYHA classification, in all cases, among subjects with both baseline and month 30 values. Data reflect observed values and do not account for missing data.

C Time to ACM or First CVH separated in favor of acoramidis by Month 3

Time to All-Cause Mortality or First Cardiovascular-Related Hospitalization Over 30 Months



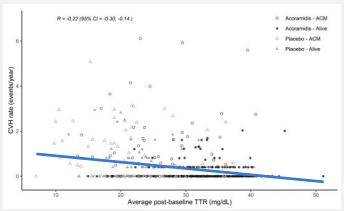
Acoramidis demonstrated **earlier and profound magnitude** of separation than demonstrated in other interventional studies of ATTR-CM to the company's knowledge

Note: mITT population. Heart transplant and implantation of cardiac mechanical assistance device were treated as death for this analysis

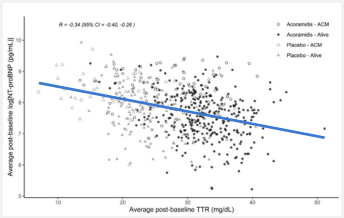
Molecular hypothesis for a second generation TTR stabilizer translated to observed benefit on measures of disease progression

Higher average serum TTR concentrations during the trial correlated significantly with benefits on morbidity and quality of life (Spearman rank correlation coefficient $p<0.0001$)

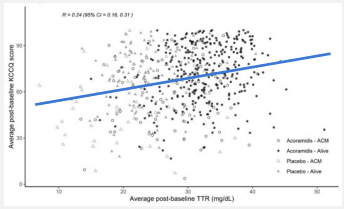
CVH Rate



NT-proBNP

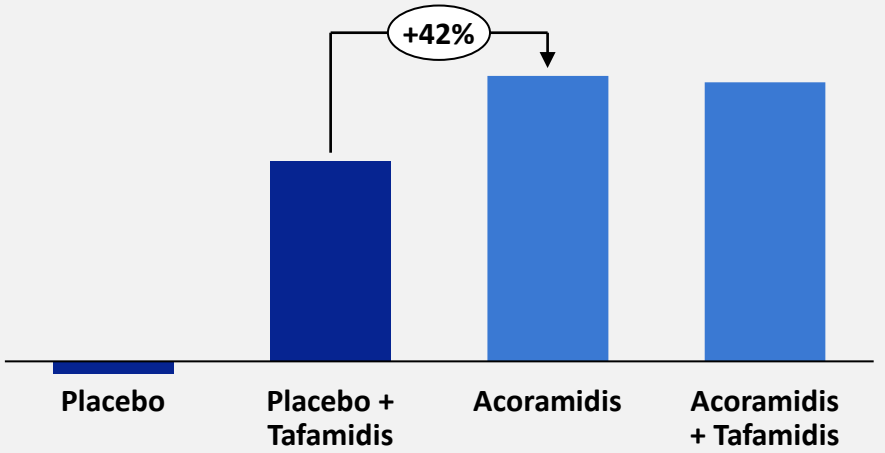


KCCQ



Near-complete TTR stabilization results in higher serum TTR levels on acoramidis

Serum TTR level at M30[2,3]



- Higher degrees of stabilization, as measured by elevated serum TTR, lead to better outcomes
- In post hoc exploratory analysis, we observed profound levels of stabilization

[1]Estimated from Damy, T., et al., Eur J Heart Fail. 2021;23(2):277-285. [2]Mean change from baseline in serum TTR at Month 30 in mITT population. [3]Mean exposure on tafamidis = 11 months in mITT population.

Discussion topics

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3. Context for clinical findings
4. **Next steps**
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First regulatory submission planned for year-end 2023

Detailed Results from ATTRibute-CM
American Heart Association 2023
November 12th, 2023

Submit New Drug Application (NDA) with FDA
End of 2023

Submit additional regulatory filings (EMA & others)
2024

Execute lifecycle management
Initiate primary prevention study (ACT-EARLY)
2024

Additional Clinical Data from ATTRibute-CM
Future medical meetings

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