#AHA23

ACORAMIDIS IMPROVES CLINICAL OUTCOMES IN TRANSTHYRETIN AMYLOID CARDIOMYOPATHY

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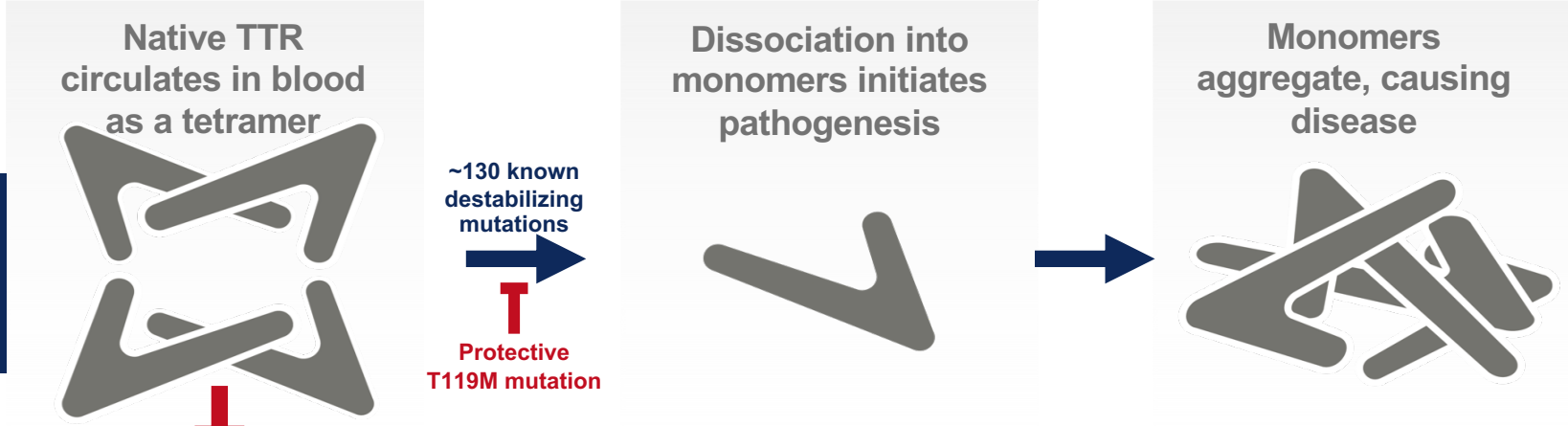
UPDATED DISCLOSURES

In the past 3 years, Daniel Judge MD has received payments as an advisor or consultant to ADRx, Alleviant Medical, Astra Zeneca, BridgeBio, Capricor, Cytokinetics, Pfizer, Novo Nordisk, and Tenaya Therapeutics.

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

ACORAMIDIS: A 2ND GENERATION, POTENT, ORAL TTR STABILIZER FOR THE TREATMENT OF ATTR-CM

Disease mechanism



Therapeutic hypothesis

Acoramidis was designed to mimic protective T119M mutation.

Phase 3 results confirm differential stabilization via effects on serum TTR.

PH. 3 STUDY (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

Key eligibility criteria

- Subjects with diagnosed ATTR-CM (WT or variant)
- NYHA Class I-III
- ATTR-positive biopsy or 99mTc scan
- Light chain amyloidosis excluded if diagnosis by 99mTc

Screening and randomization

800 mg Acoramidis HCl twice daily
N = 421

Placebo twice daily
N = 211

Efficacy assessment included 611 participants in the pre-specified mITT population (eGFR ≥30 mL/min/1.73 m²)

Tafamidis usage allowed after Month 12
(14.9% acoramidis vs. 22.8% placebo; Mean duration ~11 mo)

Open-label extension

800 mg Acoramidis twice daily

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) [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 (F-S test[1]) 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[7]	p=0.037

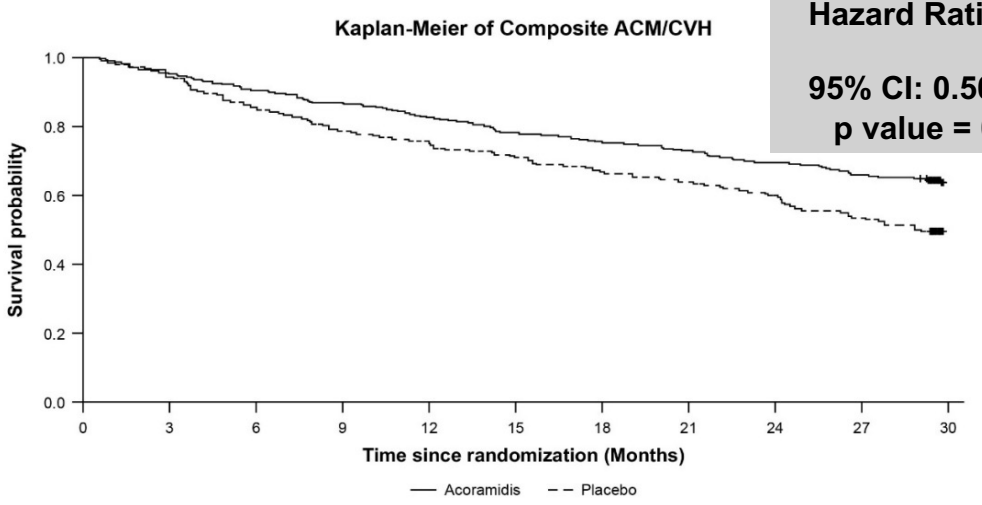
25% RRR in ACM[8]

30% RRR in CVM[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-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



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

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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)

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	

Number Needed to Treat (NNT) to prevent one CV Hospitalization per year

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CVH = Cardiovascular-related hospitalization; [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
  - 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:

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

ACM = All-Cause Mortality, CVH = Cardiovascular-Related Hospitalization, F-S: Finkelstein-Schoenfeld method

THANK YOU

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