ESC SUM:
Myocardial Diseases

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המרכז הרפואי
האוניברסיטאי הדסה
המרכז לבריאות
לב האישה על שם
לינדה ג'וי פולין

HADASSAH
UNIVERSITY
MEDICAL CENTER
LINDA JOY POLLIN
CARDIOVASCULAR
WELLNESS CENTER
FOR WOMEN

Subsequent Pregnancies in Patients with a Previous Peripartum Cardiomyopathy

A prospective study of the ESC EORP

Sliwa K, Viljoen C, Jackson A, Damasceno A, Mbanze A, Al Farhan H, Yaseen I, Mbakwem A, Dewi T, Dzielinska Z, Abdullaev T, Goland S, Hilfiker-Kleiner D, Basic M, Petrie M, Bauersachs J

Friday 25th August 2023

Peripartum Cardiomyopathy

Heart failure due to LV dysfunction, with EF <45%

Occurrence toward the end of pregnancy or in the months following delivery

No other cause of cardiomyopathy/heart failure is identified

What is the risk to mother and fetus of subsequent pregnancy?

Methods

- The PPCM EORP registry enrolled > 750 patients from 2012-2018 with a 3-year Follow-up.
- 11 sites that originally enrolled 332 patients in that Registry obtained ethics approval to participate in the sub-study on PPCM and SSP.

Results

332 patients with PPCM

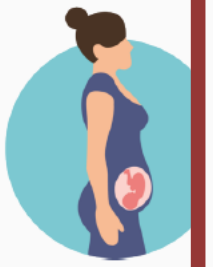
70 patients with SSP in 93 pregnancies

Median follow-up from the end of the SSP was 192 days (112-233).

Two pregnancies are still ongoing & 2 patients in follow-period

25% (23/93) pregnancies ended prematurely

- **78.2% (18/23) therapeutic termination**
- 17.4% (4/23) miscarriage
- 4.4% (1/23) stillbirth

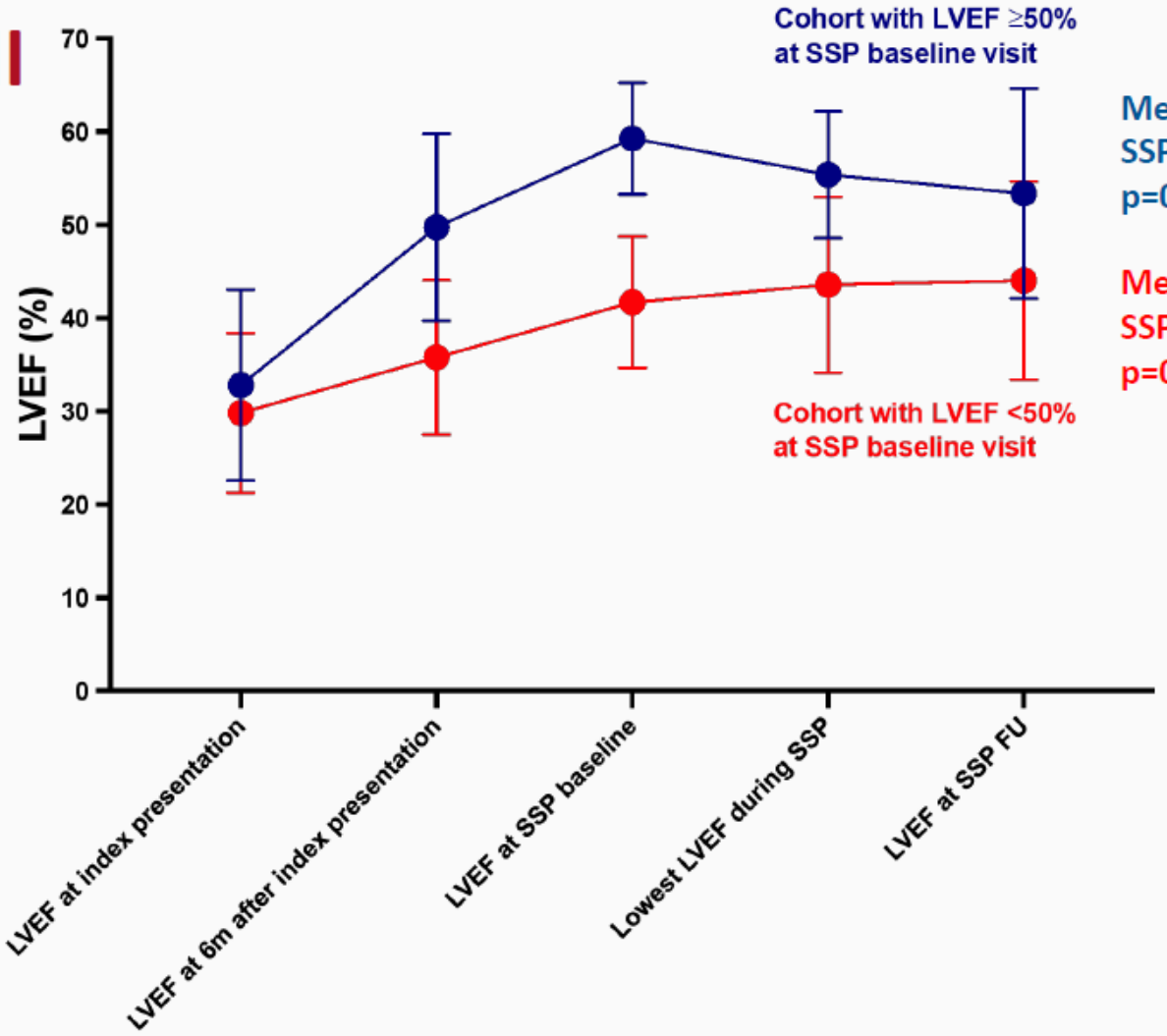


In the 70 patients with SSP of the

332 patients with PPCM

prior to SSP was present in **27% of patients**

Results III



Mean difference from SSP baseline to SSP FU: 5.2% (95% CI 1.5 to 9.0), p=0.0076

Mean difference from SSP baseline to SSP FU: -1.8% (95% CI -7.7 to 4.1), p=0.5091

Results II

** LVEF at baseline during the SSP is defined as LVEF during the first trimester (<12 weeks) or last available LVEF prior to the SSP.

*** Poor outcome was a composite defined as LVEF<50% at any point after the first trimester to the end of follow-up, or death.

	Total SSPs N=81	LVEF<50% N=22	LVEF≥50% N=59	p-value
LVEF at index presentation (%)	32.0±9.9	29.8±8.6	32.8±10.2	0.23
Last LVEF prior to SSP (%)	53.8±10.3	41.6±7.1	58.3±7.1	<0.001
LVEF at SSP baseline (%) **	54.5±10.1	41.7±7.0	59.3±6.0	<0.001
Follow-up LVEF (%)	51.0±11.7	44.0±10.6	53.4±11.3	0.020
Follow-up LVEF ≥50%	31 (72.1)	5 (45.5)	26 (81.2)	0.022
All-cause death	1 (1.6)	1 (6.7)	0 (0.0)	0.077
Poor outcome ***	19 (31.7)	10 (62.5)	9 (20.5)	0.002

- Poor outcome (composite endpoint of LVEF <50% [at any time after the first trimester to the end of follow-up] or death) was encountered by 32% with 1% mortality (due to a stroke- 1 week postpartum).
- There were no differences in age, parity or prevalence of smoking between women with good or poor outcome, but hypertension was more common in the poor outcome group (25% vs 0%).
- Persistently reduced LVEF prior to the SSP was associated with lower rates of full recovery at the final follow-up.

Conclusion

- In this ongoing registry of PPCM with a subsequent pregnancy, we found a lower-than-expected mortality.
- Persistently impaired LV systolic function (LVEF<50% prior to the SSP) was associated with higher rates poor outcome and of LVEF<50% at final follow-up.
- Notably, the only death in this study occurred in this group.

Efficacy and Safety of Mavacamten in Chinese Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

EXPLORER
MAVACAMTEN CHINA PHASE II

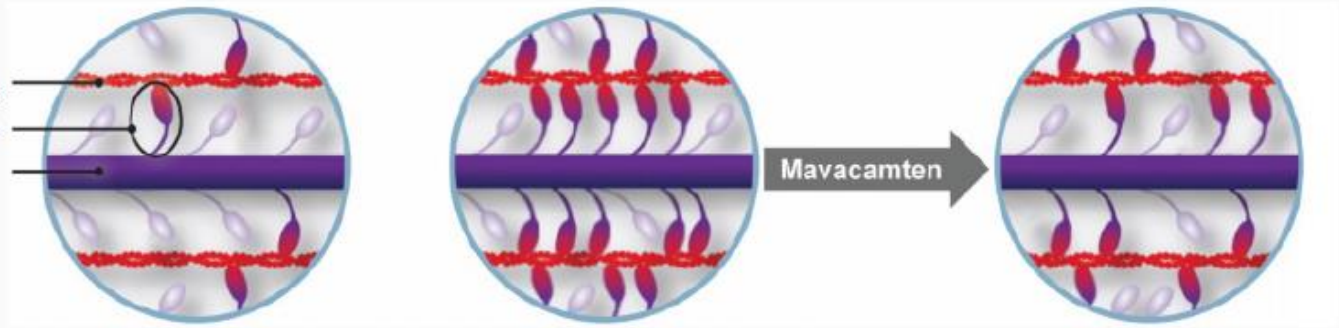
Results of the EXPLORER-CN Study

Zhuang Tian, MD[1]; Liwen Li, MD[2]; Xiaoyan Li, MD[3]; Jian'an Wang, MD[4]; Qing Zhang, MD[5]; Zhanquan Li, MD[6]; Daoquan Peng, MD[7]; Ping Yang, MD[8]; Wei Ma, MD[9]; Fang Wang, MD[10]; Wei Jin, MD[11]; Xiang Cheng, MD[12]; Shuyang Zhang, MD[1]

[1]Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2]Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, Guangdong Province, China; [3]Renmin Hospital of Wuhan University, Hubei General Hospital, Wuhan, Hubei Province, China; [4]Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China; [5]West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [6]People's Hospital of Liaoning Province, Shenyang, Liaoning Province, China; [7]Second Xiangya Hospital of Central South University, Changsha, Hunan Province, China; [8]China-Japan Union Hospital of Jilin University, Changchun, Jilin Province, China; [9]Peking University First Hospital, Beijing, China; [10]Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China; [11]Ruijin Hospital, Shanghai Jiaotong University, School of Medicine, Shanghai, China; [12]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei Province, China

August 28, 2023

Mavacamten: Mechanism of Action



Normal Sarcomere

Normal contraction
Effective relaxation

HCM Sarcomere

HCM Pathophysiology:

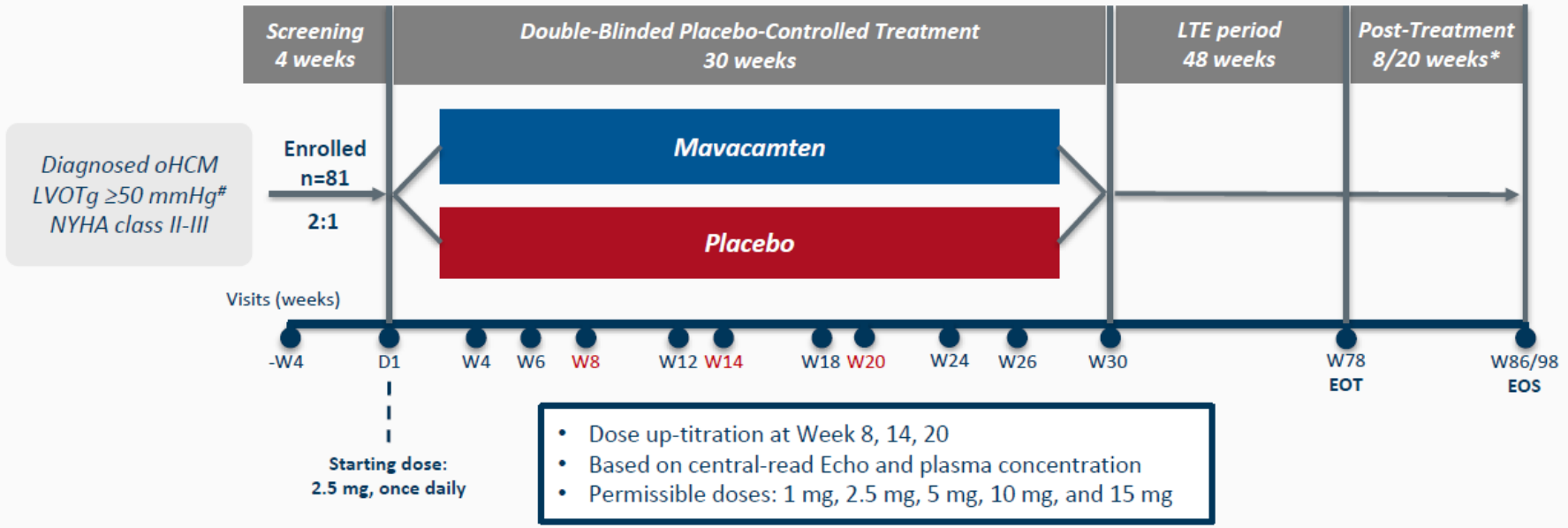
- Hypercontractility
- Impaired relaxation
- Altered myocardial energetics

HCM Sarcomere with Mavacamten

- Attenuated hypercontractility
- Improved relaxation
- Improved energetics

Mavacamten is a first-in-class, targeted inhibitor of cardiac myosin, reduces the number of myosin-actin cross-bridges and thus decreases excessive contractility characteristic of HCM.

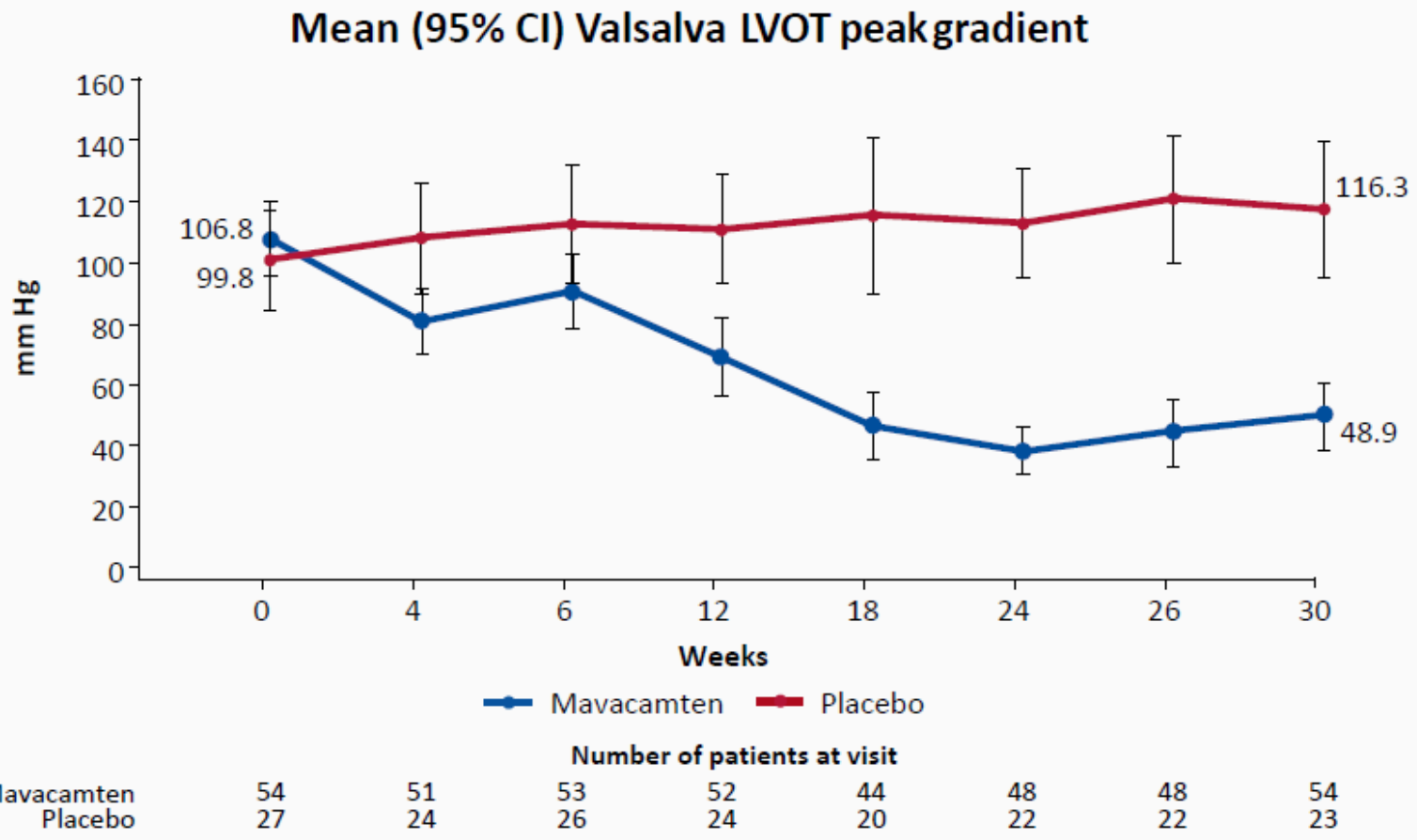
EXPLORER-CN Study Design



*Post treatment follow-up period: 8 weeks (or 20 weeks for poor CYP2C19 metabolizer)
#LVOT peak gradient ≥ 50 mmHg at rest or after Valsalva maneuver during screening

Primary Efficacy Endpoint

EXPLORE



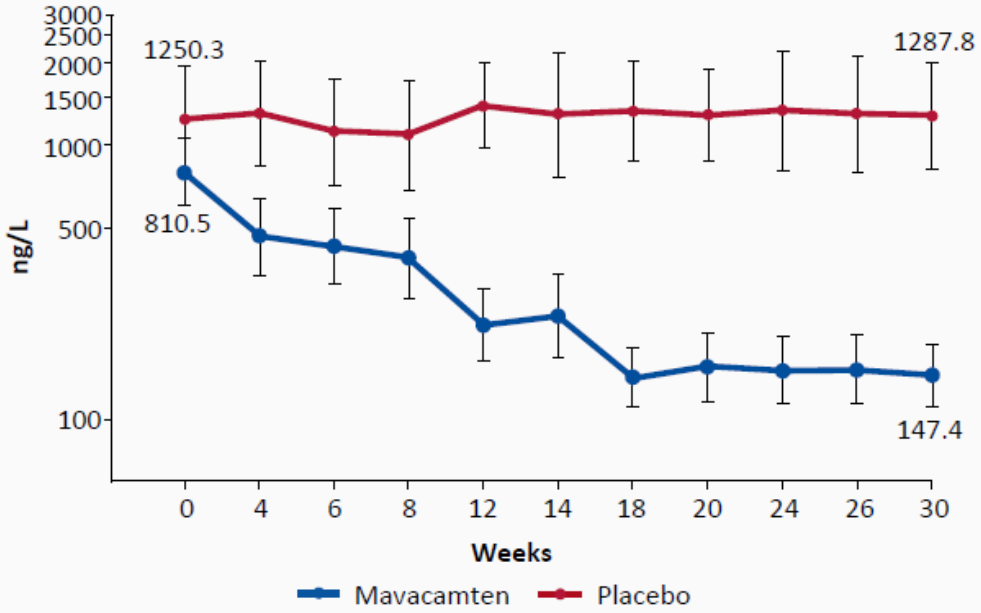
Change from baseline to Week 30 in Valsalva LVOT peak gradient:

LSM difference: -70.29 mmHg, 95% CI: -89.64, -50.94, 1-sided *P* value <0.001

Cardiac Biomarkers Over Time

EXPLORER-CN

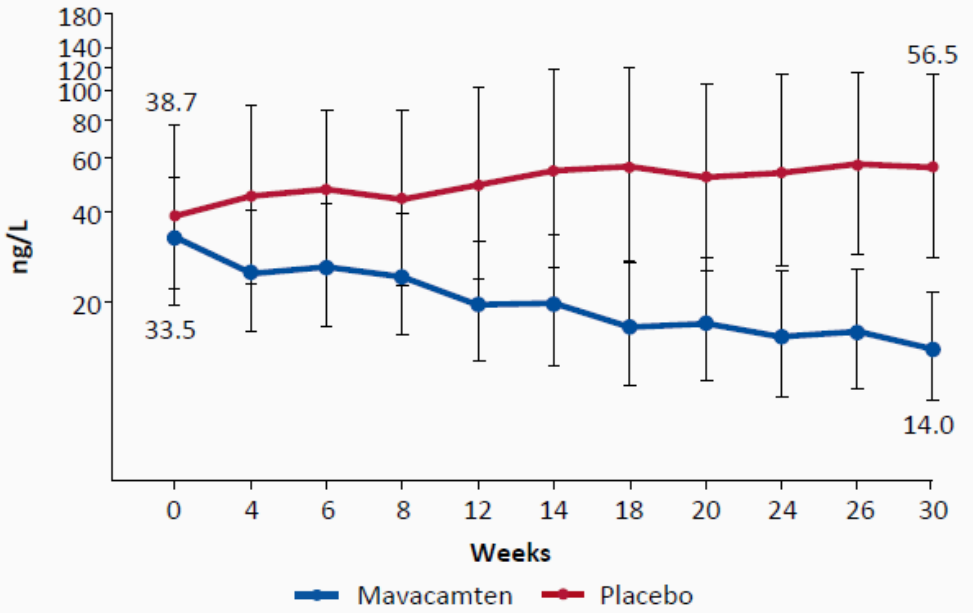
Geometric mean (95%CI) NT-proBNP



Number of patients at visit

Mavacamten	54	54	53	51	51	50	48	48	47	49	54
Placebo	27	26	27	26	24	22	22	23	23	24	24

Geometric mean (95%CI) hs-cTnI



Number of patients at visit

Mavacamten	54	54	52	51	51	50	48	47	47	49	54
Placebo	27	26	27	26	24	22	22	23	23	24	24

CI, confidence interval; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Secondary Efficacy Endpoints

EXPLORER

	Mavacamten (n=54)	Placebo (n=27)	Difference (95% CI)#	*P* value&
Change from baseline to Week 30 in Resting LVOT peak gradient, mmHg, mean (SD)	-51.45 (35.99)	6.38 (34.36)	-54.99 (-69.13, -40.86)	**<0.001**
Proportion of participants achieving a Valsalva LVOT peak gradient <30 mmHg at Week 30, n (%)	26 (48.1)	1 (3.7)	0.41 (0.24, 0.57)	**<0.001**
Proportion of participants achieving a Valsalva LVOT peak gradient <50 mmHg at Week 30, n (%)	32 (59.3)	2 (7.4)	0.47 (0.30, 0.64)	**<0.001**
Proportion of participants with at least 1 class improvement in NYHA functional classification from baseline to Week 30, n (%)	32 (59.3)	4 (14.8)	0.39 (0.20, 0.58)	**<0.001**
Change from baseline to Week 30 in KCCQ-CSS, mean (SD)	5.70 (15.426)	-5.37 (11.519)	10.24 (4.35, 16.13)	**<0.001**
Change from baseline to Week 30 in NT-proBNP, GMR (%CV)	0.18 (92.31)	0.93 (57.93)	0.18 (0.13, 0.24)	**<0.001**
Change from baseline to Week 30 in hs-cTnI, GMR (%CV)	0.42 (47.05)	1.24 (77.58)	0.34 (0.27, 0.42)	**<0.001**
Change from baseline to Week 30 in LVMI (CMR), g/m^2, mean (SD)*	-26.37 (21.06)	4.43 (14.42)	-30.80 (-41.55, -20.05)	**<0.001**

* CMR set: mavacamten n=39, placebo n=19

Model estimated least-square mean differences were reported for continuous variables. Common risk difference with 95% CI based on the stratified Miettinen-Nurminen method were reported for category variables. Proportion of geometric mean ratio Mavacamten/Placebo was reported for NT-proBNP and hs-cTnI.

& Nominal p-values are presented for descriptive purpose. No hypothesis testing was pre-specified for secondary efficacy endpoints.

Summary of Safety During 30-week DBPC Period

	Mavacamten (n=54)	Placebo (n=27)
Participants with ≥1 TEAE, n (%)	45 (83.3)	24 (88.9)
Participants with ≥1 related TEAE, n (%)	11 (20.4)	9 (33.3)
Participants with ≥1 severe TEAE#, n (%)	1 (1.9) [1]	0
Total Numbers of TESAEs	8	0
Participants with ≥1 TESAE, n (%)	4 (7.4)	0
Atrial fibrillation [1,2]	2 (3.7)	0
Atrial flutter[3]	1 (1.9)	0
Sinus arrest [2]	1 (1.9)	0
Sinus node dysfunction [2]	1 (1.9)	0
Hypotension [1]	1 (1.9)	0
Haemorrhoids[4]	1 (1.9)	0
Ankle fracture [1]	1 (1.9)	0
Participants with ≥1 related TESAE, n (%)	0	0
Participants with ≥1 AESI, n (%)	1 (1.9)[5]	0

- There were 4 (7.4%) participants in the mavacamten group reported TESAEs.
- All TESAEs were assessed as not related to study drug by the investigator.
- There were no TEAEs leading to dose interruption, discontinuation of study drug or the study.
- There were no TEAEs leading to death.

[1] One participant experienced 1 severe TESAE of ankle fracture and 2 life-threatening TESAEs of atrial fibrillation (had prior history) and hypotension. [2] One participant experienced 3 moderate TESAEs of sinus arrest, atrial fibrillation (no prior history) and sinus node dysfunction. [3] One participant experienced 1 moderate TESAE of atrial flutter (no prior history). [4] One participant experienced 1 mild TESAE of hemorrhoids. [5] One participant experienced 2 AESIs of symptomatic overdose and pregnancy termination of gestational partner.
A severe TEAE is defined as a TEAE with a severity of "severe", "life-threatening" or "fatal". An AE with missing severity is classified as severe.

Temporary Treatment Discontinuation

Participants Who Met Temporary Treatment Discontinuation Criteria that Trigger IxRS Alerts*

Criteria	Mavacamten (n=54)	Placebo (n=27)
Resting LVEF <50% by Core Laboratory	0	0
Pre-dose Plasma Drug Concentration ≥ 1000ng/mL	1 (1.9%)	0
Both	0	0

- There was one participant in the mavacamten group who had dose interruption due to pre-dose plasma drug concentration ≥ 1000 ng/mL. The dose level before interruption was 10 mg at Week 24, and predose plasma concentration was 1010 ng/ml. The LVEF was 75%.
- The patient remained asymptomatic throughout and mavacamten was subsequently resumed at the 5 mg dose.
- No participant had dose interruption due to LVEF < 50%.

Conclusions

- Mavacamten works similarly in the Chinese population
- Safety profile was similar, with no new safety signals

Myosin Inhibition in Patients with Obstructive HCM Referred for Septal Reduction Therapy

Week 56 results of the VALOR-HCM Trial

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ESC Congress

VALOR-HCM

Phase III placebo-controlled RCT (for 16 weeks) with placebo to mavacamten cross over starting Week 16

Sought to determine if addition of mavacamten to maximally-tolerated medical therapy would allow severely symptomatic oHCM patients to improve sufficiently that they no longer met guideline criteria for SRT or chose not to undergo SRT

Principal Objective of Week 56 VALOR-HCM

Report the safety and efficacy results through 56 weeks of dose-blinded treatment in patients initially randomized to mavacamten (Day 1 to Week 56) and patients initially randomized to placebo who crossed over to mavacamten for 40 weeks exposure (Week 16 to Week 56)

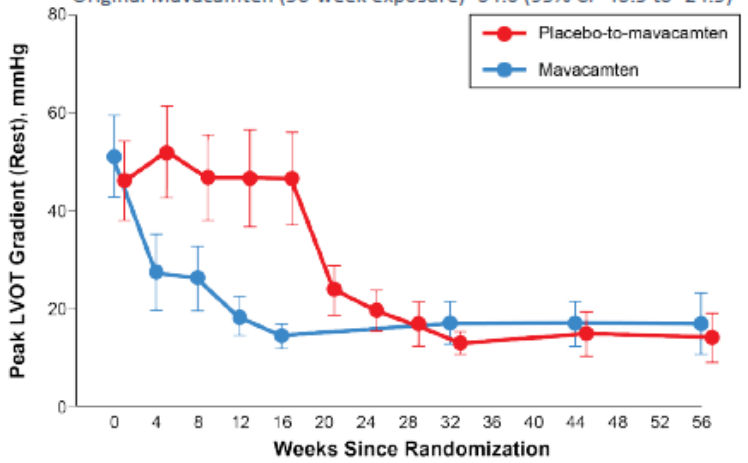
Key inclusion criteria

- Age ≥18 years
- Documented HCM with maximum septal wall thickness ≥15 mm or ≥13 mm with family history of HCM (determined by a core echo laboratory)
- Severe symptoms despite maximally-tolerated medical therapy
  - NYHA functional Class III/IV or Class II with exertional syncope or near syncope
  - Maximal medical HCM therapy could include disopyramide and/or combination therapy
- Dynamic LVOT gradient at rest or with provocation (Valsalva maneuver or exercise) ≥50 mmHg
- Documented LV ejection fraction ≥60%
- Must have been referred within the past 12 months for SRT and actively considering scheduling the procedure
  - Patients could elect to proceed to SRT at any time following randomization

Sustained Improvement in Efficacy Endpoints

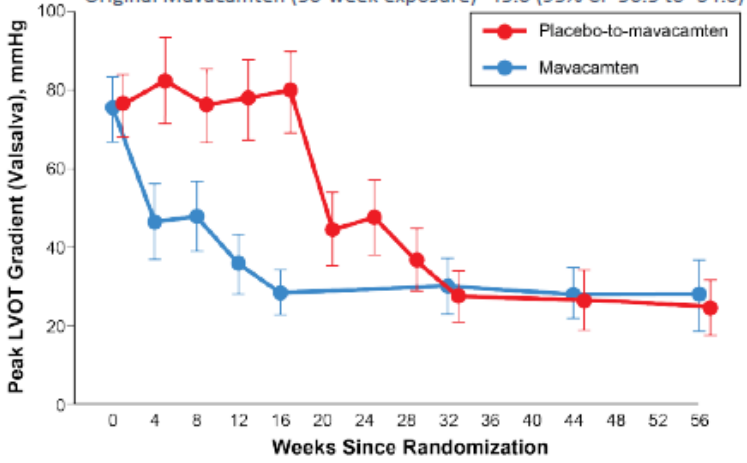
Resting LVOT Gradient

Original Placebo (40-week exposure) -33.2 (95% CI -41.9 to -24.5)
Original Mavacamten (56-week exposure) -34.0 (95% CI -43.5 to -24.5)



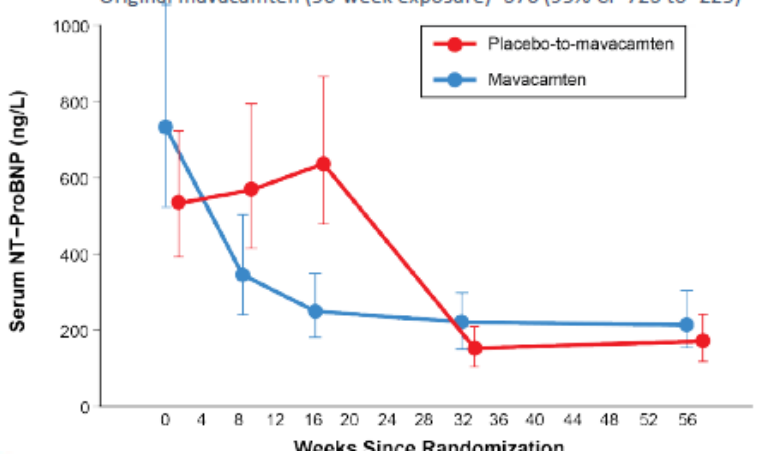
Valsalva LVOT Gradient

Original Placebo (40-week exposure) -54.6 (95% CI -66.0 to -43.3)
Original Mavacamten (56-week exposure) -45.6 (95% CI -56.5 to -34.6)



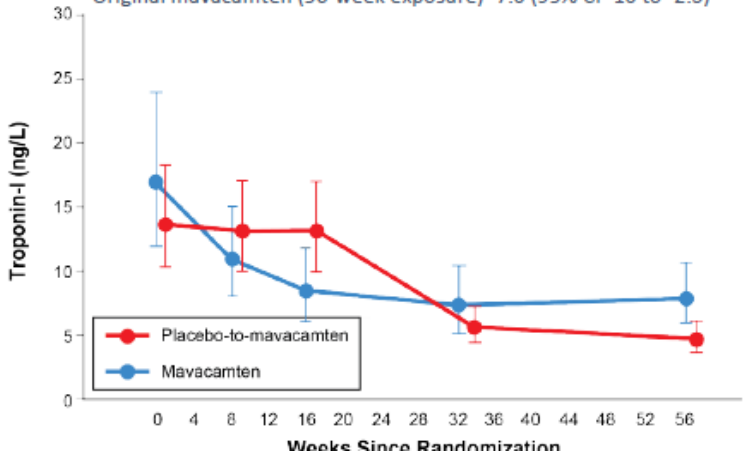
NT-ProBNP

Original placebo (40-week exposure) -423 (95% CI -624 to -252)
Original mavacamten (56-week exposure) -376 (95% CI -723 to -225)



Troponin I

Original placebo (40-week exposure) -6.2 (95% CI -11.5 to -3.3)
Original mavacamten (56-week exposure) -7.0 (95% CI -10 to -2.3)

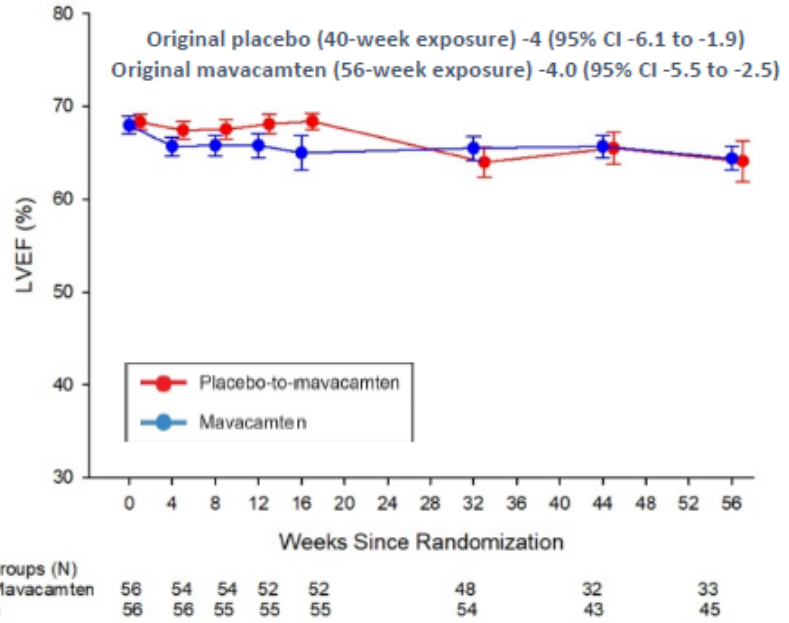


Selected safety endpoints at Week 56

ValorHCM

Characteristic	Placebo-to-mavacamten (40 weeks exposure) N=52	Original mavacamten (56 weeks exposure) N=56	Total mavacamten N=108
Safety endpoints			
Permanent study drug discontinuation a) LVEF <30% b) Two consecutive LVEF measurements of < 50% despite dose reduction to 2.5 mg	2 (3.8) 1 (1.9)	0 0	3 (2.8)
One Temporary Interruption for LVEF (>30% to <50%)	2 (3.8)	7 (12.5)	9 (8.3)
Total with ANY LV EF (<50%)	5 (9.6)	7 (12.5)	12 (11.1)
Cardiac death	1 (1.9)*	0	
Heart failure hospitalization	1 (1.9)¥	0	
Selected serious treatment-emergent adverse events			
At least one serious treatment-emergent adverse event	6 (11.5)	4 (7.1)	10 (9.3)
Atrial fibrillation	0	3 (5.4)	3 (2.8)
Congestive heart failure	1 (1.9)	0	1 (0.9)
Ventricular arrhythmia	1 (1.9)	0	1 (0.9)
Drug administration site reaction	2 (3.8)	0	2 (1.9)
COVID-19	0	1 (1.8)	1 (0.9)

LV Ejection fraction



9/12 (75%) patients with LVEF < 50% were asymptomatic and able to resume mavacamten at a lower dose, after temporary interruption

* This patient had a site-reported LV ejection fraction of 30% and mavacamten was discontinued.
¥ This patient was admitted for congestive heart failure with concomitant atrial fibrillation and had a core-lab reported LV ejection fraction < 30%. Mavacamten was permanently discontinued.

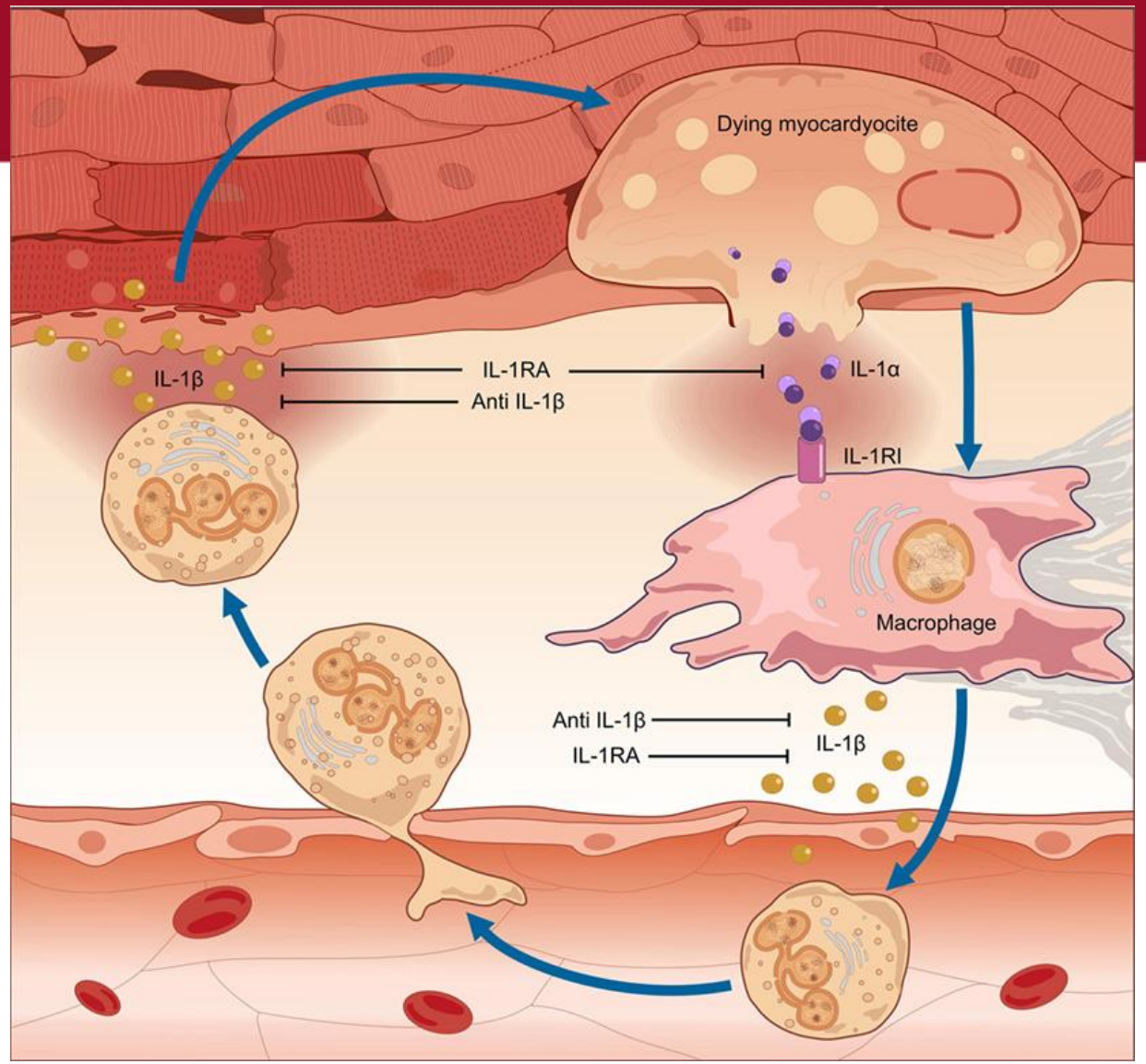
- Efficacy and safety similar to what was previously reported
- No sex differences
- Dosage was guided by echo rather than by core lab or pharmacokinetics-similar to “real world”

The ARAMIS trial

Anakinra versus Placebo, a Double Blind Randomized Controlled Trial, for the Treatment of Acute Myocarditis

Mathieu Kerneis, MD, PhD; Fleur Cohen, MD, PhD; Alain Combes, MD, PhD; Eric Vicaut MD, PhD; Gilles Montalescot, MD, PhD

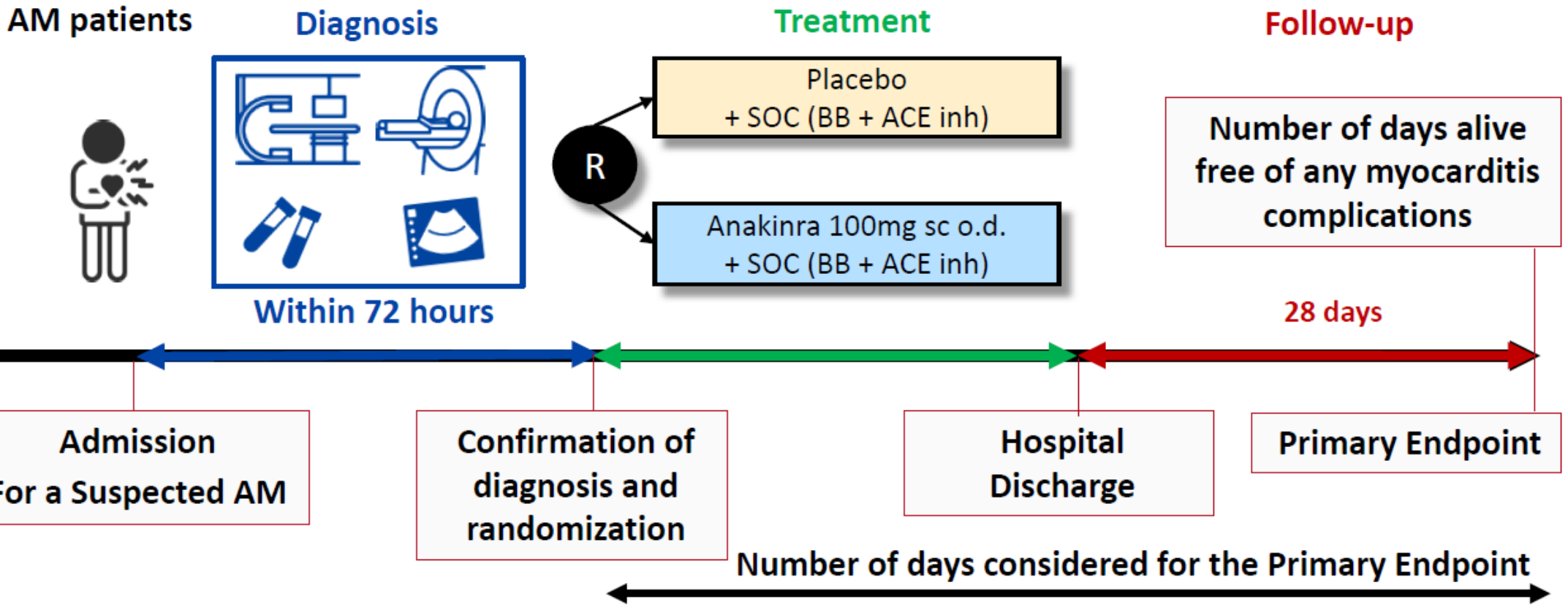
On Behalf of the ARAMIS investigators



IL-1α is released from the dying myocardiocytes, together with intracellular debris and inflammatory mediators; these in turn activate a molecular complex known as the “inflammasome,” resulting in processing and release of active IL-1β by infiltrating inflammatory cells. Runaway cardiac inflammation ensues, leading to apoptosis of cardiomyocytes and loss of contractile tissue, cardiomyopathy, and heart failure.

Study Design of the ARAMIS Trial

Randomized, Double Blind, Multicenter, Phase IIb trial



Inclusion/Exclusion Criteria

Inclusion

Myocarditis was defined as follows :

Chest Pain

AND modification of the ECG *or* elevated Troponin (at least 1.5 X ULN)

AND CMR Lake Louise Criteria

AND Normal Coronary angiography or CTA in > 40 y/o *or* with CV risk factors

Exclusion

< 18 y/o or > 65 y/o

LV assistance

Mechanical Ventilation

Any clinical suspicion of autoimmune, giant cell, eosinophilic, or sarcoidosis related myocarditis

Renal Failure

Anti-TNF, CTC/NSAID use

Malignancy

Endpoints

@28 days post hospitalization discharge

Efficacy = Number of days alive free of any myocarditis complications

- **Heart Failure** requiring hospitalization
- **Chest Pain** requiring an additional medication
- **LVEF < 50%** in TTE
- **Ventricular arrhythmia** (VT or VF)

Safety = SAEs including those potentially related to the drug :

- Severe infection
- ALT/AST > 10x ULN
- Neutropenia < 1. 109/L
- Renal failure (↑ 50% creat)
- Thrombopenia < 50 000 mm3
- BARC> 3
- Anaphylactic reaction
- 100% ↑ of LDL Cholesterol

Clinical Presentation (1/2)

	Anakinra N=57	Placebo N=60
Median Age, (Q1;Q3), yrs	28.0 (22.8 ; 38.1)	29.0 (23.2 ; 34.0)
Male — no of patients (%)	52 (91.2%)	50 (83.3%)
Current smoker — no. (%)	30 (52.6%)	30 (50.0%)
Past Medical History		
Prior myocarditis — no. (%)	1 (1.8%)	3 (5.0%)
Recent Bacterial infection— no. (%)		
Recent Viral infection — no. (%)		
Chest Pain — no.(%)		
Dyspnea — no. (%)		
Cardiogenic shock — no. (%)		
Ventricular fibrillation — no. (%)		
Conduction disorders — no. (%)		
Clinical infectious syndrome — no. (		

Non Invasive Imaging

	Anakinra N=57	Placebo N=60
Left ventricular ejection fraction (TTE), %		
Median (Q1;Q3)	60 (50;61)	60 (50;60)
Min, Max	40, 73	35, 66
Ventricular dysfunction with TTE (LVEF<50%) — no. (%)	7 (12.3%)	5 (8.3%)
Regional wall motion abnormalities (TTE) — no. (%)	18 (31.6%)	16 (26.7%)
Left ventricular ejection fraction (MRI), %		
Median (Q1;Q3)	54 (50;60)	55 (52;60)
Min, Max	36, 72	38, 70
Ventricular dysfunction with MRI (LVEF<50%) — no. (%)	13 (22.8%)	10 (16.7%)

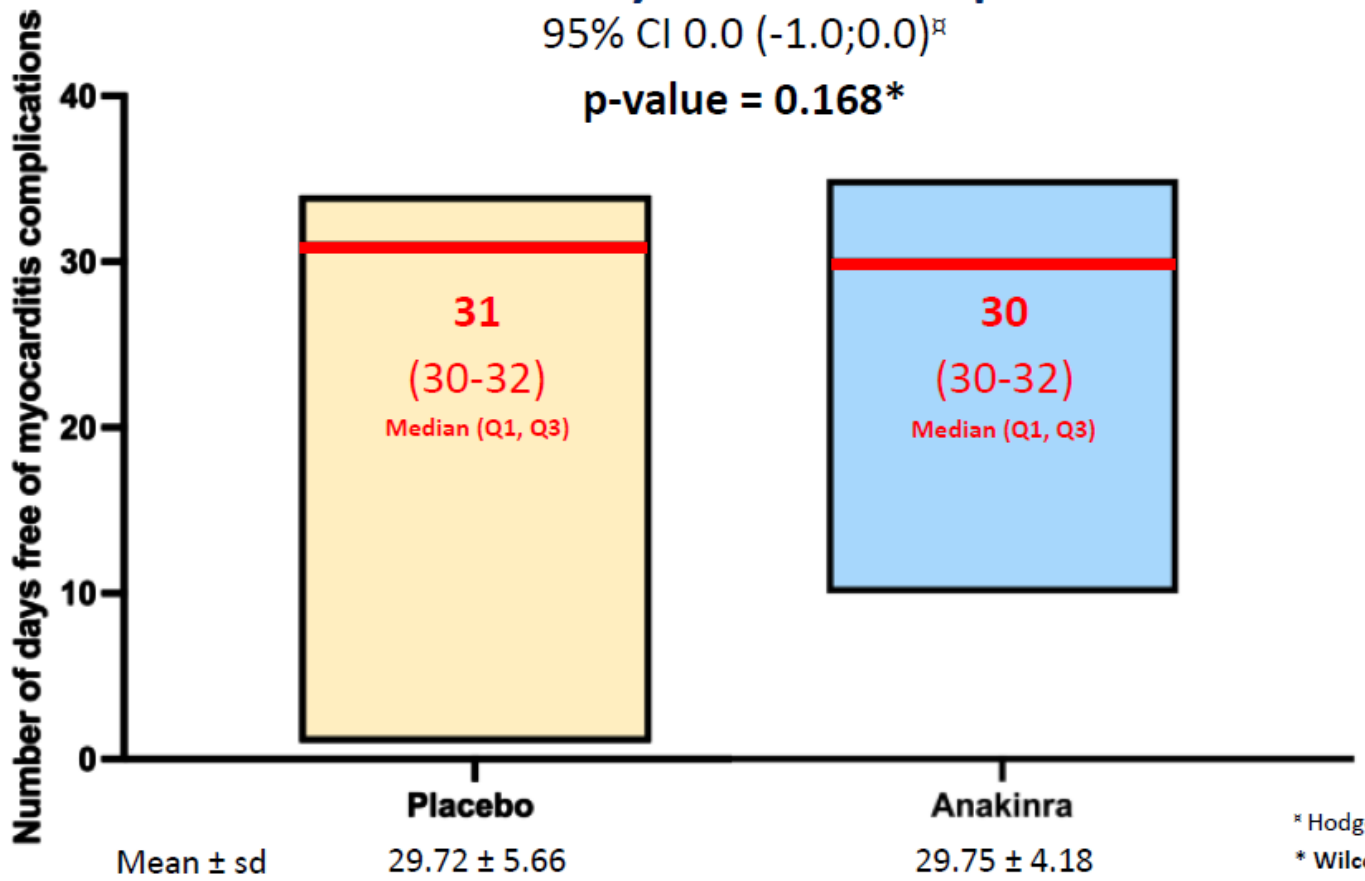
Absence of pericardial effusion — no. (%)	48 (85.7%)	47 (78.3%)

Primary Endpoint

Number of days free of complications

95% CI 0.0 (-1.0;0.0)¤

p-value = 0.168*



Red Line = Median

Box = Min-Max

¤ Hodges-Lehmann's median difference

*** Wilcoxon-Mann Whitney test**

Non parametric Ancova p-value = 0.192

Clinical Events

All events were adjudicated by an independent CEC blinded to the randomization groups

	Anakinra N=57	Placebo N=60	Odds Ratio (95% CI)
Composite outcome * @28 days post discharge **— no. (%)**	**6 (10.5%)**	**10 (16.7%)**	**0.59 (0.19; 1.78)**
Heart Failure	0	0	-
Ventricular arrhythmia	1 (1.8%)	1 (1.7%)	-
Chest pain requiring new medication	2 (3.5%)	6 (10.0%)	0.33 (0.06; 1.76)
Ventricular dysfunction (LVEF<50%)	4 (8.5%)	4 (7.4%)	1.16 (0.27; 5.09)

***HF, ventricular arrhythmia, chest pain requiring medication or LVEF<50% at 28 days post discharge — no. (%)**

ARAMIS, the largest RCT in acute myocarditis, enrolled for the first time an all-comer **acute** myocarditis population diagnosed on **CMR**, mostly at **low risk of events.**

A short administration of anakinra did **not increase the number of days free of myocarditis complications**

There was no safety issue with anakinra administered during the acute phase of myocarditis diagnosed without EMB (**no proof of absence of viral replication**)

Further RCT studies are needed to explore the potential benefit of the anti-inflammatory strategy in acute myocarditis patients at **higher risk of events**

Larger studies are needed to evaluate **prolonged anti inflammatory strategies** in acute myocarditis patients at « low-to-moderate risk » (16% of events at M1)

TAKE HOME MESSAGE

ARAMIS showed the FEASIBILITY of trials in the setting of ACUTE MYOCARDITIS, and even if neutral, important data are still missing (i.e. change in LVEF and change in troponin).

ARAMIS reflects the REALITY and it is the first randomized clinical trial (RCT) to recruite patients with **acute myocarditis** diagnosed by **CMR+troponin**.

Most patients with acute myocarditis are at **low risk of events.**

Further larger RCT studies are needed to explore the potential benefit of ANAKINRA/other immunosuppressive drugs in acute myocarditis patients at **higher risk of events**

Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

Results of the ATTRibute-CM Trial

Julian D. Gillmore,[1] Daniel P. Judge,[2] Francesco Cappelli,[3] Marianna Fontana,[1] Pablo Garcia-Pavia,[4,5,6] Simon Gibbs,[7] Martha Grogan,[8] Mazen Hanna,[9] James Hoffman,[10] Ahmad Masri,[11] Mathew S. Maurer,[12] Jose Nativi-Nicolau,[13] Laura Obici,[14] Frank Rockhold,[15, 16] Keyur B. Shah,[17] Prem Soman,[18] Jyotsna Garg,[15] Karen Chiswell,[15] Haolin Xu,[15] Xiaofan Cao,[19] Ted Lystig,[19] Uma Sinha,[19] and Jonathan C. Fox[19]

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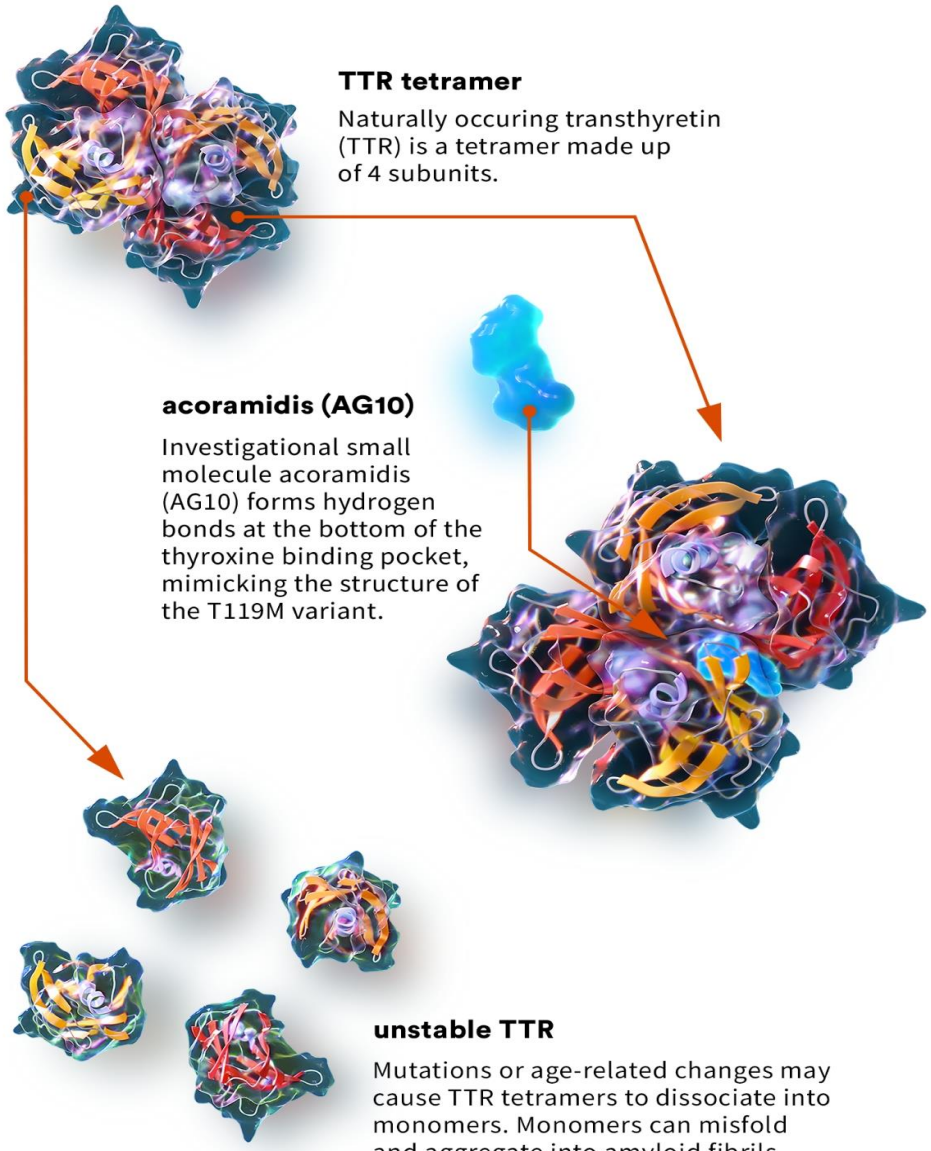
27 Aug 2023

ESC Congress 2023
Amsterdam & Online

about acoramidis (AG10)



TTR tetramer

Naturally occuring transthyretin (TTR) is a tetramer made up of 4 subunits.

acoramidis (AG10)

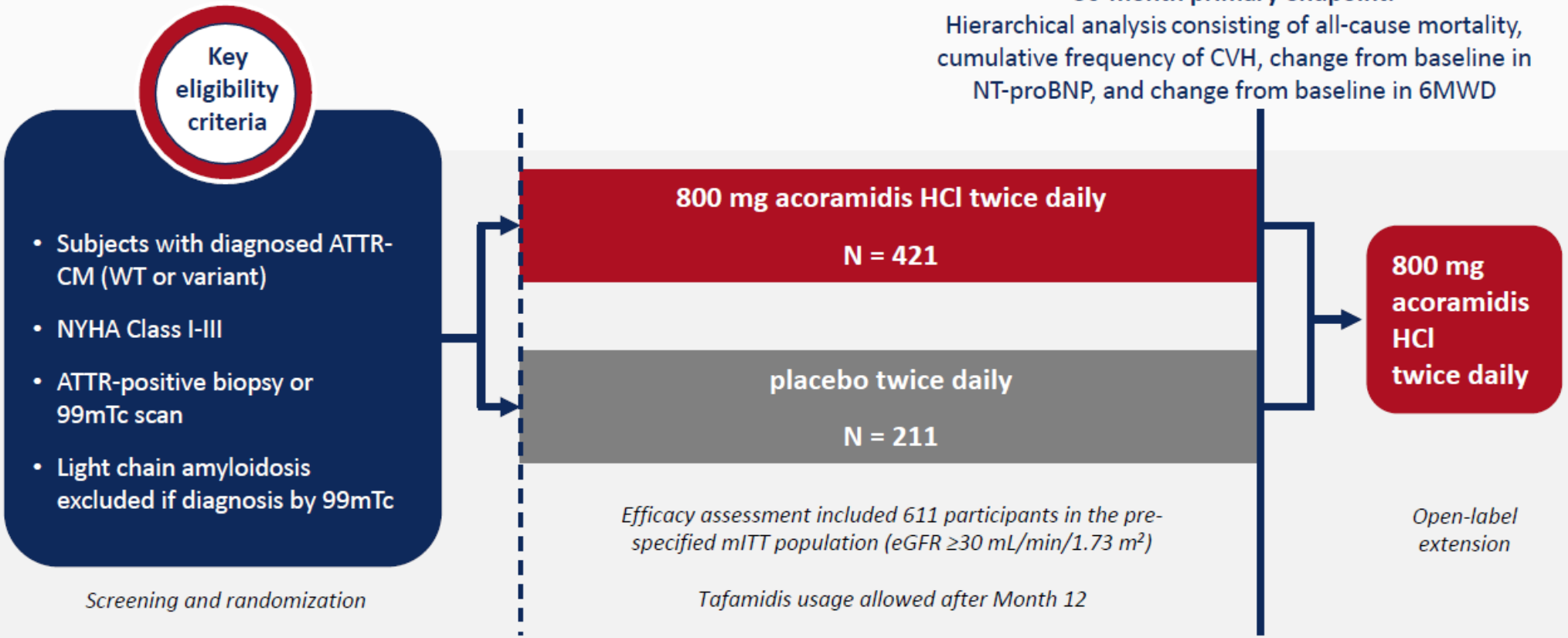
Investigational small molecule acoramidis (AG10) forms hydrogen bonds at the bottom of the thyroxine binding pocket, mimicking the structure of the T119M variant.

unstable TTR

Mutations or age-related changes may cause TTR tetramers to dissociate into monomers. Monomers can misfold and aggregate into amyloid fibrils, which may deposit in various organs.

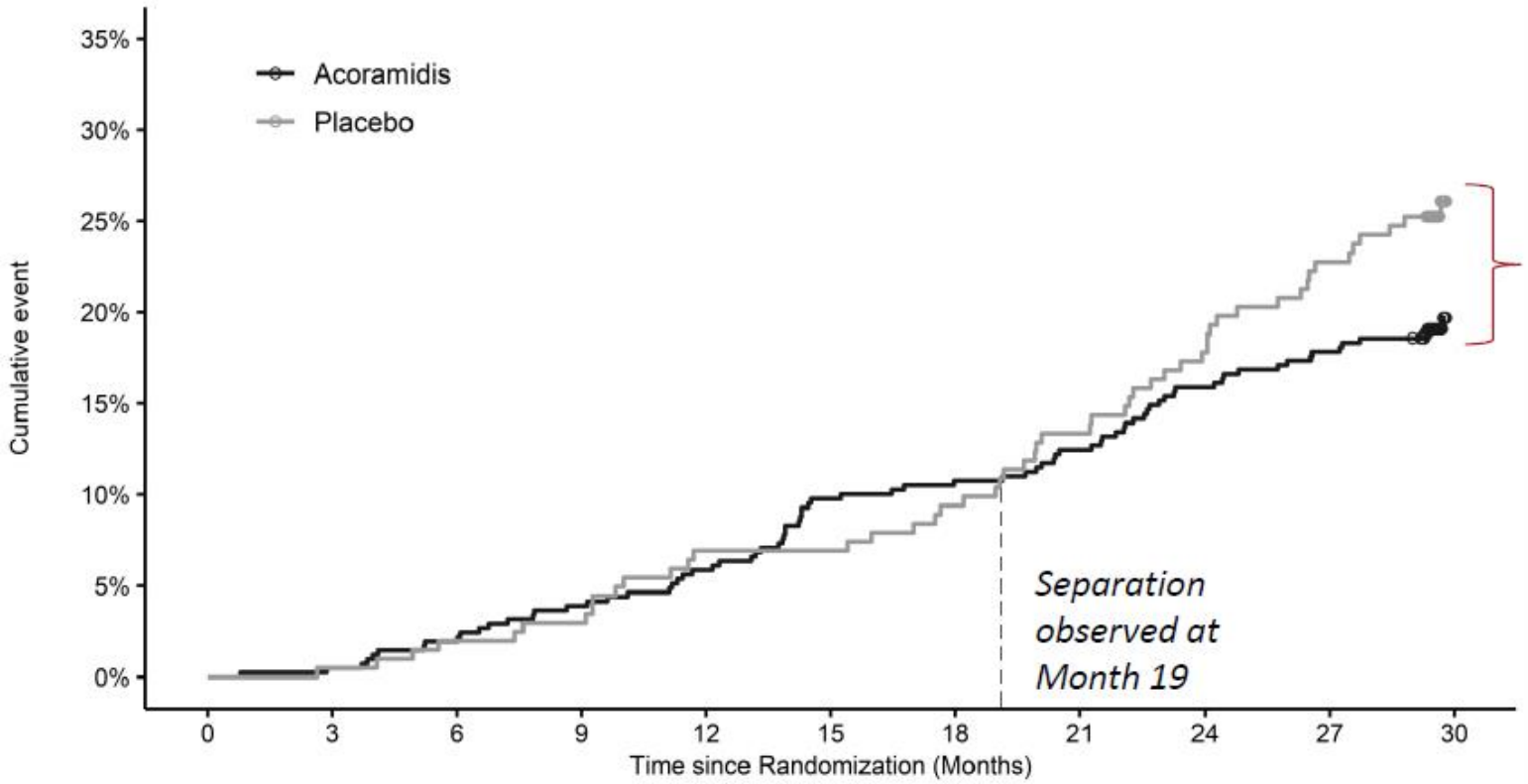
ATTRibute-CM: Study Design

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: All-Cause Mortality

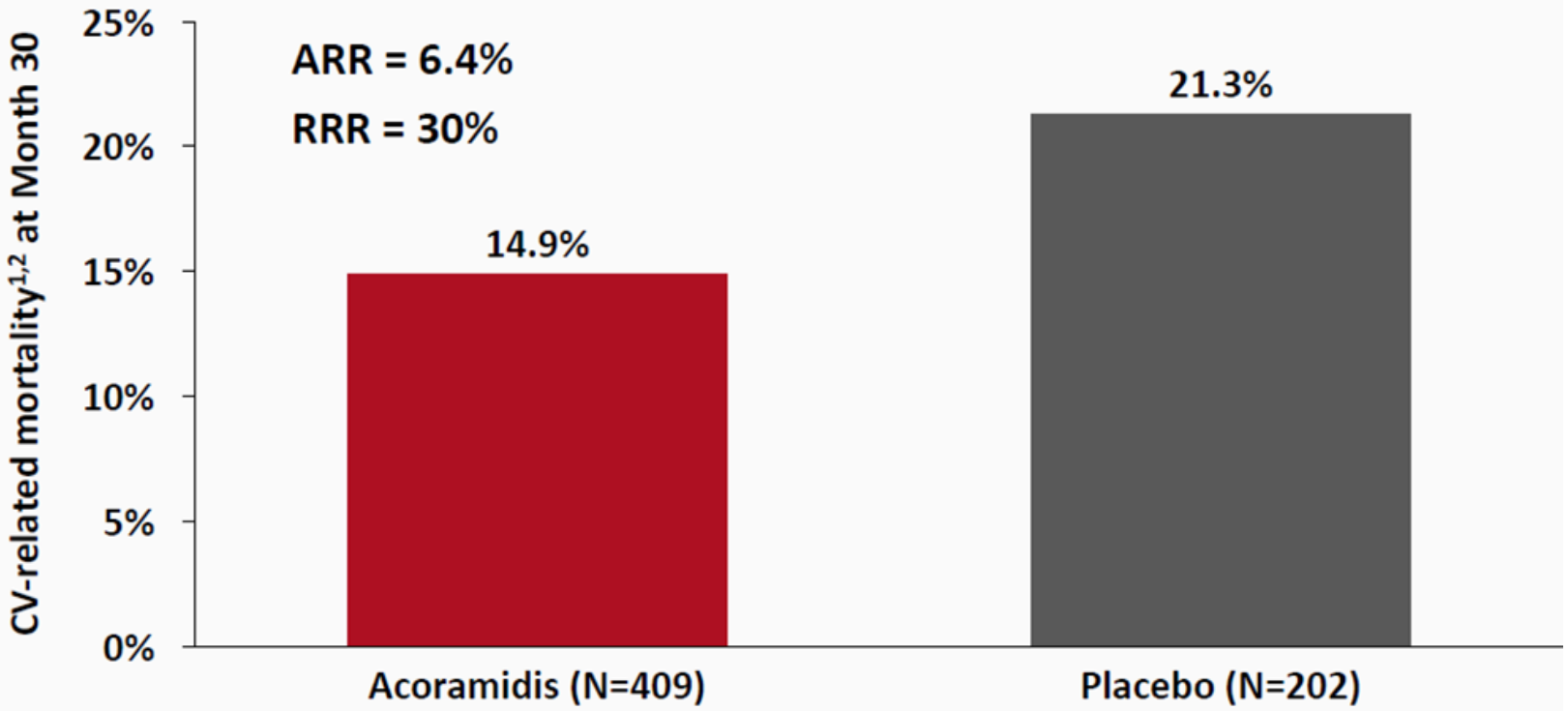


Number at risk (number of events)

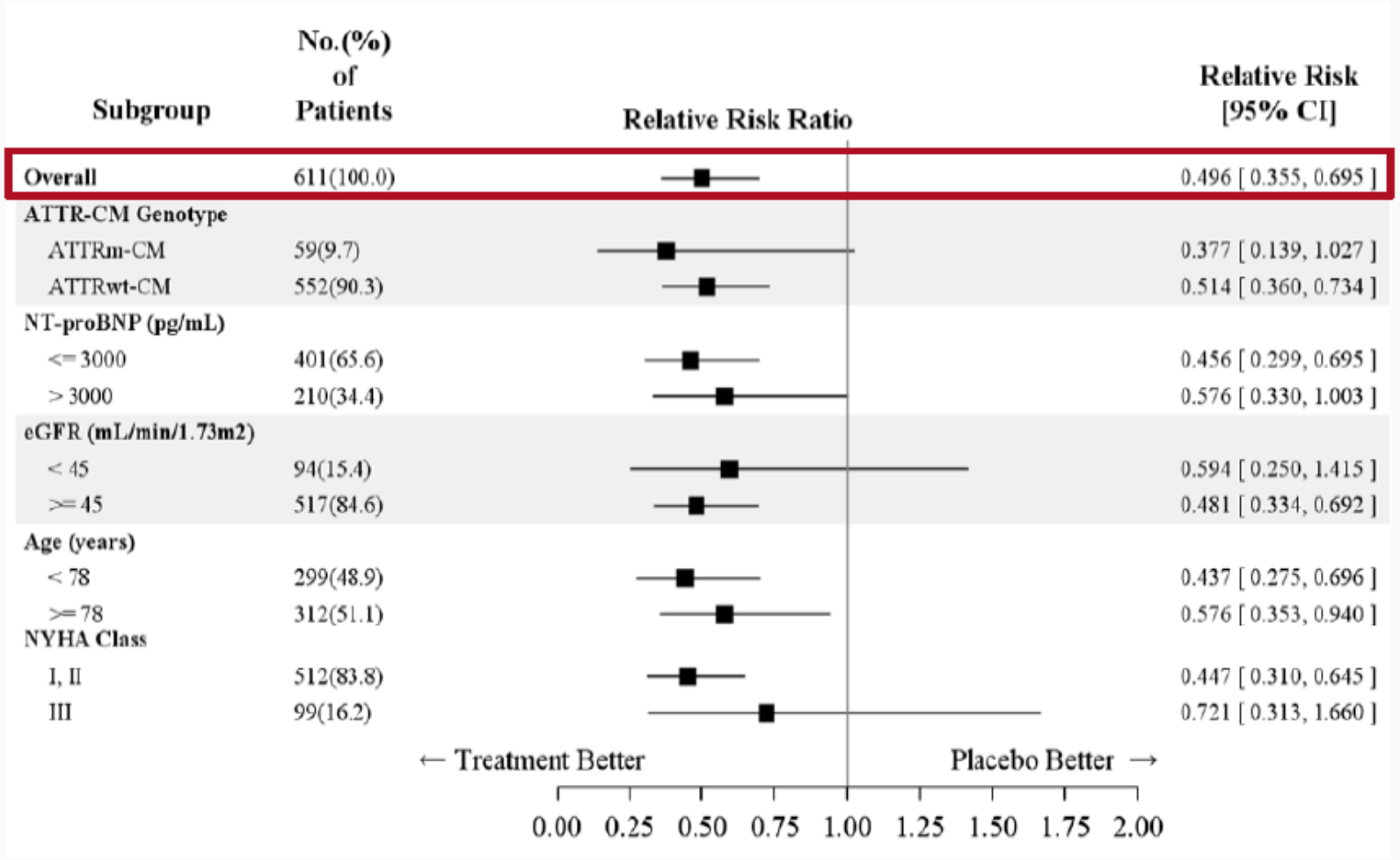
Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)

ARR = Absolute risk reduction; RRR = Relative risk reduction; HR = Hazard ratio.
All-cause mortality includes heart transplant, implantation of cardiac mechanical assist device, and all-cause death.

ATTRibute-CM: Cardiovascular-Related Mortality



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



ATTRibute-CM: Patient Safety

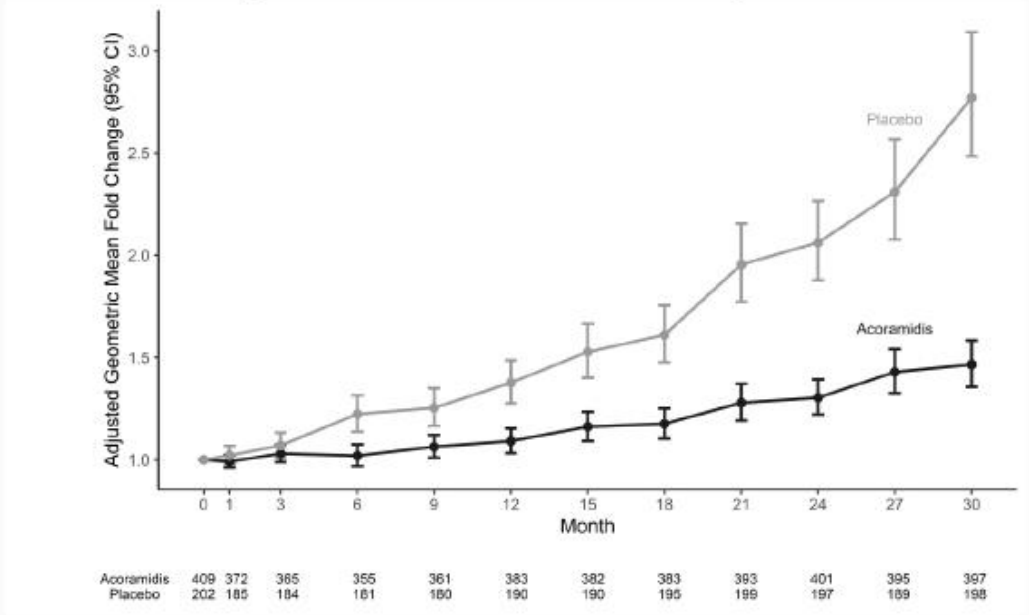
Subjects with one or more event(s)	Acoramidis N=421 N (%)	Placebo N=211 N (%)
Any treatment-emergent adverse events (TEAEs)	413 (98.1%)	206 (97.6%)
TEAE with fatal outcome	60 (14.3%)	36 (17.1%)
TEAE leading to hospitalization	212 (50.4%)	128 (60.7%)
TEAE leading to study drug discontinuation	39 (9.3%)	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

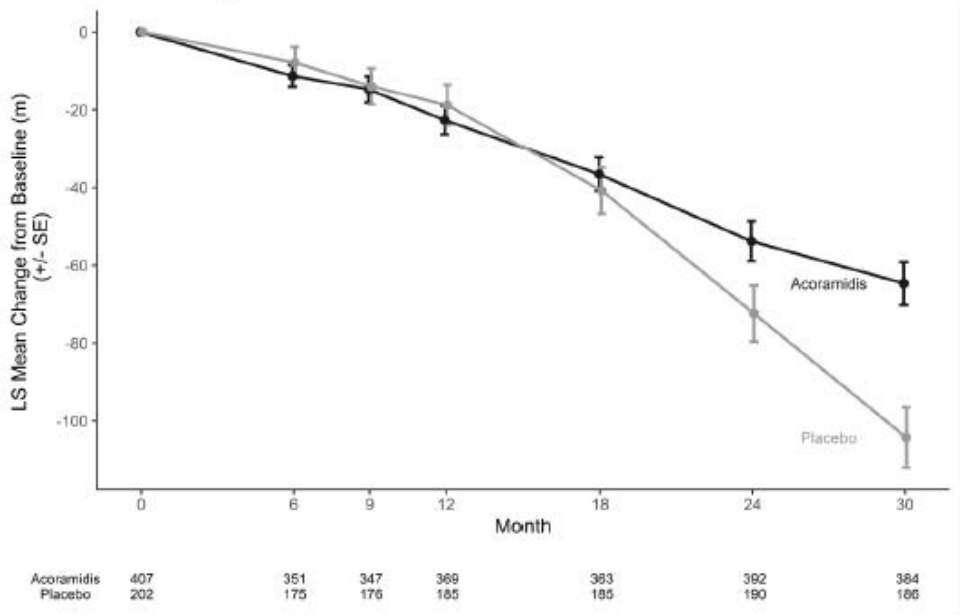
All Adverse Events (AEs) occurring during the treatment period are considered treatment-emergent adverse events (TEAEs). Serious Adverse Event (SAE) meets seriousness criteria.
[1]Severity as assessed by the investigator.

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

Change from Baseline in NT-proBNP[1]



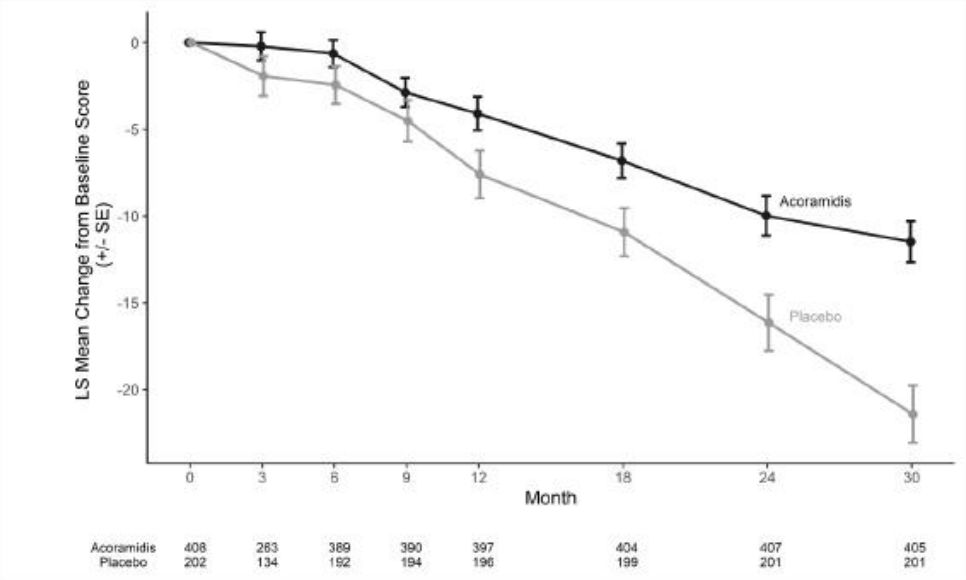
Change from Baseline in 6MWD[1]



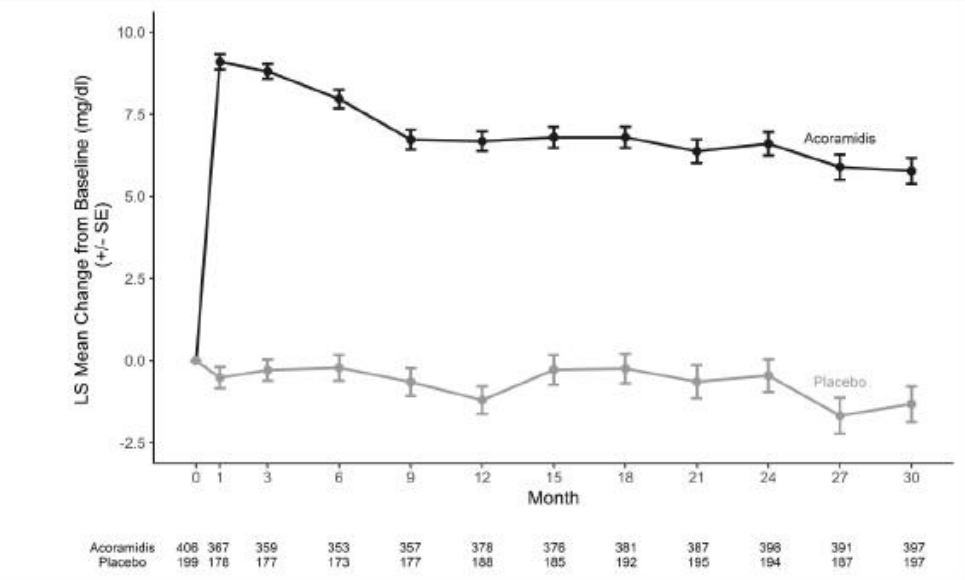
[1]Analyzed using mixed effects model with repeated measures. Missing measurements due to early discontinuation imputed using the Jump to Reference method. Missing measurements due to death performed by sampling with replacement from bottom 5% of observed values.

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

Change from Baseline in KCCQ-OS[1]



Change from Baseline in Serum TTR



[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: 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 key secondary endpoints**
  - Better preservation of exercise 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 cohort (~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.

Comparisons of Baseline Demographic Characteristics: ATTRIBUTE and ATTR-ACT

	ATTRIBUTE CM		ATTR-ACT	
Characteristic	**Acoramidis**	**Placebo**	**Tafamidis**	**Placebo**
N	421	211	264	177
Age (years), mean (SD)	77.4 (6.5)	77.1 (6.8)	74.5 (7.2)	74.1 (6.7)
Male sex, n (%)	384 (91.2)	186 (88.2)	241 (91.3)	157 (88.7)
ATTRwt-CM, n(%)	380 (90.3)	191 (90.5)	201 (76.1)	134 (75.7)
NT-proBNP (pg/mL), median (IQR)	2326 (1332, 4019)	2306 (1128, 3754)	2996 (1751 – 4861)	3161 (1864 – 4825)
NYHA 1	512 (83.8) (from slide 5)		24 (9.1)	13 (7.3)
NYHA 2			162 (61.4)	101 (57.1)
NYHA 3	99 (16.2)		78 (29.5)	63 (35.6)

- **Are the differences of age, NYHA class, ATTR-CM type explain by the difference of hard outcome impact between the two drugs?**

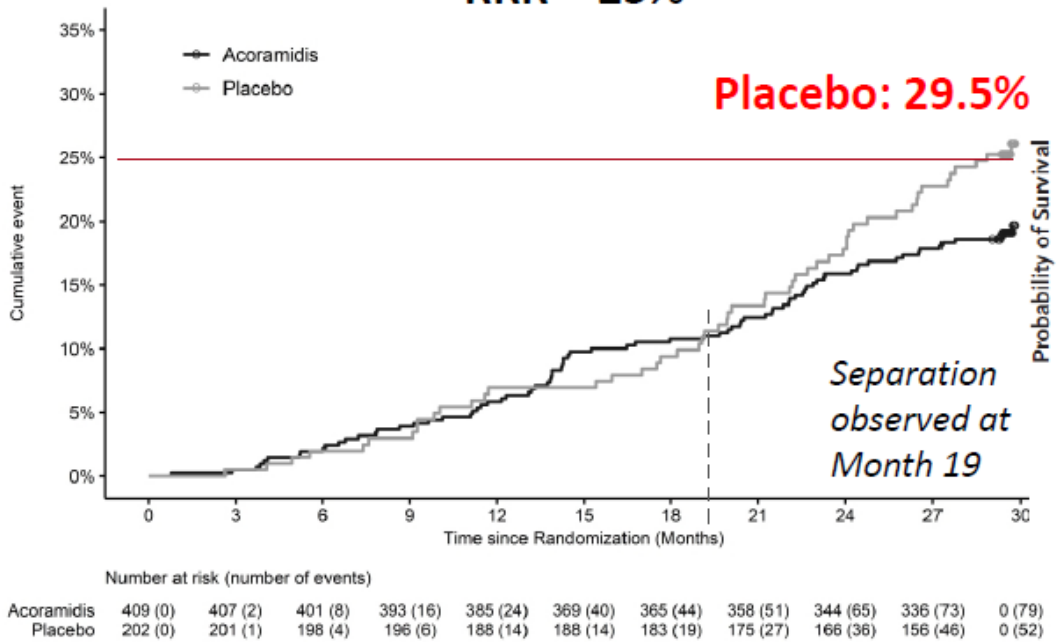
ATTRwt-CM = Transthyretin amyloidosis wild-type cardiomyopathy; NT-proBNP = N-terminal pro-B-type natriuretic peptide; IQR = interquartile range; TTR = transthyretin; KCCQ-OS = Kansas City cardiomyopathy questionnaire overall summary score.
*Tafamidis usage allowed after Month 12.

Comparison of all-Cause Mortality in the placebo group in the two trials

ATTRibute-CM

ARR = 6.4%

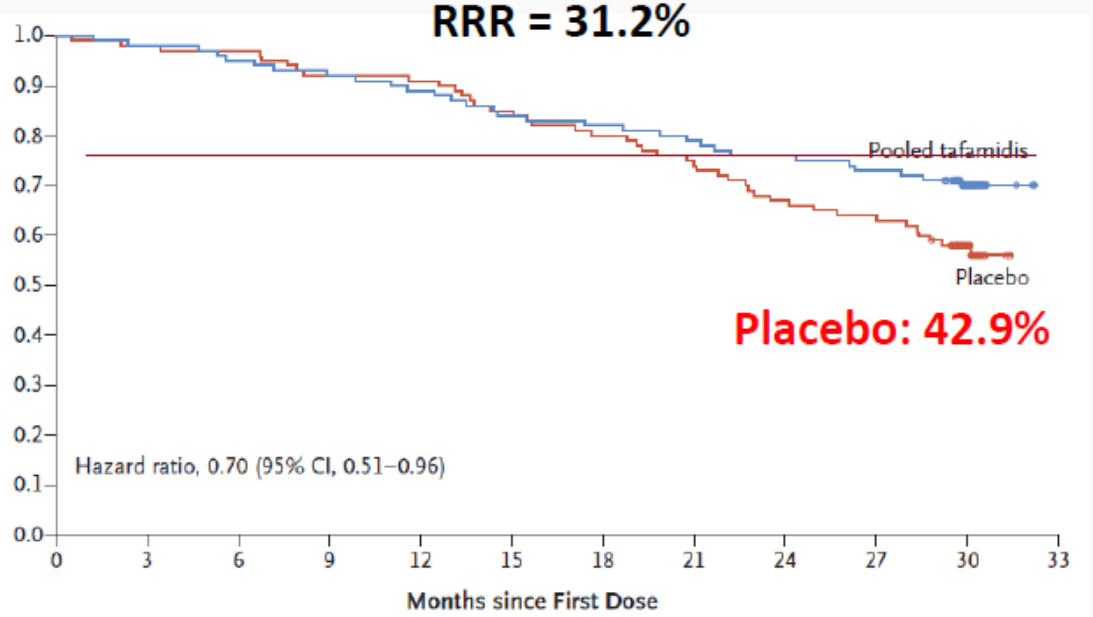
RRR = 25%



ATTR-ACT

ARR = 13.4%

RRR = 31.2%



- Patients included in ATTRIBUTE-CM have less severe ATTR-CM and better prognosis but…

What will be the role of acoramadis?

תודה על ההקשבה

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