CUPID 2: A Phase 2b Trial Investigating the Efficacy and Safety of the Intracoronary Administration of AAV1/SERCA2a in Patients with Advanced Heart Failure

917 – Hot Line V – Heart Failure
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On Behalf of the CUPID 2 Trial Investigators & Executive Steering Committee

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DECLARATION OF INTEREST

- Consulting/Royalties/Owner/ Stockholder of a healthcare company

Disclosures

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CUPID 2 Committees

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- Javed Butler
- G. Michael Felker
- Piotr Ponikowski
- Adriaan Voors

Data Monitoring Committee

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- Piotr Ponikowski, Poland
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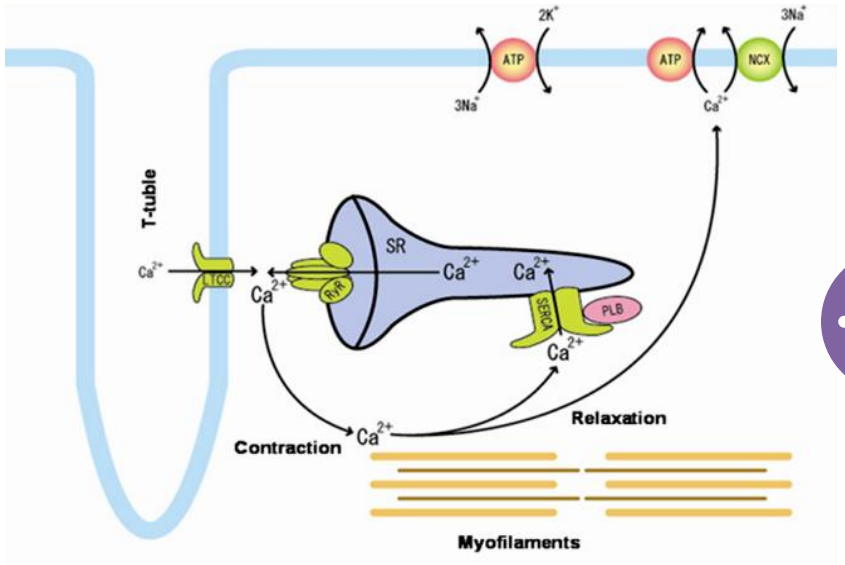
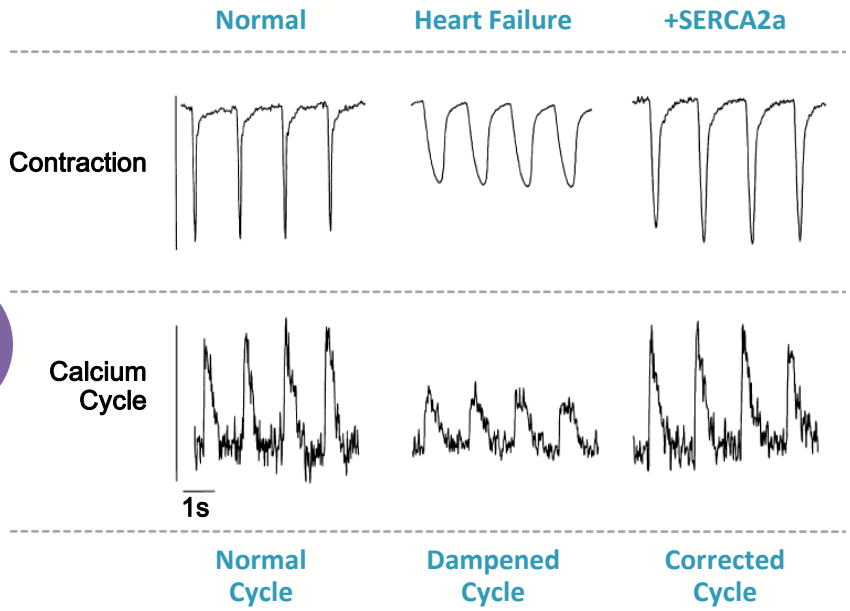
BACKGROUND

SERCA2a Deficiency is Central to the Progression of Heart Failure





SERCA2a: A Critical Enzyme
Responsible for Driving the Pumping Action of the Heart and Becomes Deficient in Patients with Heart Failure

Restoration in End-Stage Human Heart Cells
Can Restore Normal Contractility, Relaxation and Calcium Cycling

*J Am Coll Cardiol. 2008;51:1112-1119; J Mol Cell Cardiol. 2007;42:852-861; Byrne M, et.al. Gene Ther. (24 Jul 2008); Surg Clin N Am 84 (2004) 141–159

Rationale for CUPID 2

- Gene transfer with AAV1/SERC2a has been shown to improve cardiac performance and outcomes in a variety of experimental models
- A Phase 1/Phase 2a study in heart failure patients (CUPID 1) suggested that AAV1/SERCA2a stabilized or improved several independent measures of patient wellbeing and cardiac function and that it was associated with a reduction in the recurrent heart failure event rate compared to a placebo-treated control population
- CUPID 2 study was designed to confirm the beneficial effects of the percutaneous intra-coronary administration of AAV1/SERCA2a on clinical outcomes in patients with moderate to severe heart failure symptoms and reduced ejection fraction and to assess the safety of this approach

METHODS – CUPID 2

Main Inclusion and Exclusion Criteria

Inclusion

- 18-80 years of age
- Diagnosis of NYHA Class II-IV chronic HF due to ischemic or non-ischemic cardiomyopathy
- LVEF ≥ 0.35
- Optimal tolerated stable medical therapy for ≥30 days
- Elevated natriuretic peptide or history of HF-related hospitalization within 6 months of enrollment
- <1:2 or equivocal anti-AAV1 neutralizing antibody

Exclusion

- Hypertrophic, restrictive and obstructive cardiomyopathy; acute myocarditis; amyloidosis; discrete LV aneurysm
- Cardiac surgery, PCI, valvuloplasty or IV therapy for HF within 30 days prior to screening
- Surgically implanted LVAD
- Significant liver or renal impairment (>3x ULN; GFR ≤20 mL/min/1.73 m^2)
- History of cancer within the past 5 years
- Active infection

Greenberg B, Yaroshinsky A, Zsebo KM, et al. J Am Coll Cardiol HF 2014;2:84.92

AAV1/SERCA2a Administered Via Percutaneous Intracoronary Artery Perfusion

- One time antegrade epicardial coronary artery infusion over 10 minutes
- Infusion pump & commercially available guide or diagnostic catheters
- 60 mL divided into 1, 2 or 3 infusions depending on anatomy
- Nitroglycerin just prior to infusion (5 µg/min titrated up to MTD)
- Aim was to provide diffuse homogenous left ventricular exposure to AAV1/SERCA2a

Endpoints

Primary Efficacy Endpoint: Time to recurrent HF-related hospitalizations and ambulatory WHF in presence of terminal events (all-cause death, transplant, dMCS)

Secondary Efficacy Endpoint: Time to first terminal event (all-cause death, transplant, dMCS)

Exploratory Endpoints: NYHA class, NT-proBNP, 6MWT & KCCQ QOL

Safety Endpoints: Disposition, clinical events; AEs including procedure-related AEs; changes in medications, vital signs & weight, physical exam, 12-lead ECG, ICD & lab parameters; time to CV-related death

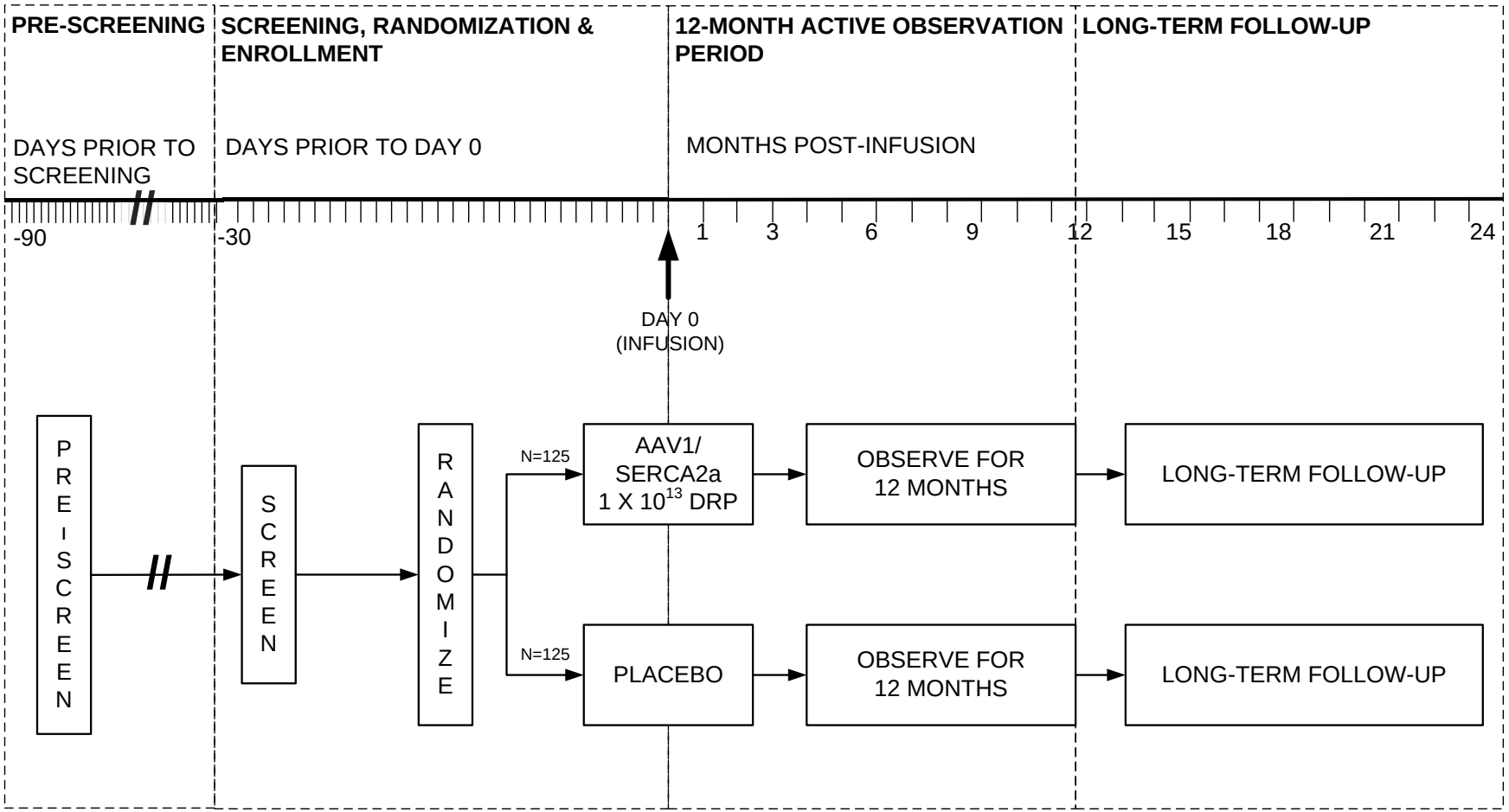
Greenberg B, Yaroshinsky A, Zsebo KM, et al. J Am Coll Cardiol HF 2014;2:84.92

Sample Size Calculations

- Monte Carlo simulation performed using background rates and correlations similar to those observed in CUPID 1:
  - 186 recurrent events in 250 patients with a median follow-up time of 18 months
  - 80% power at the 0.05 two-sided significance level
  - To detect a recurrent event hazard ratio of 0.55 using a joint frailty model

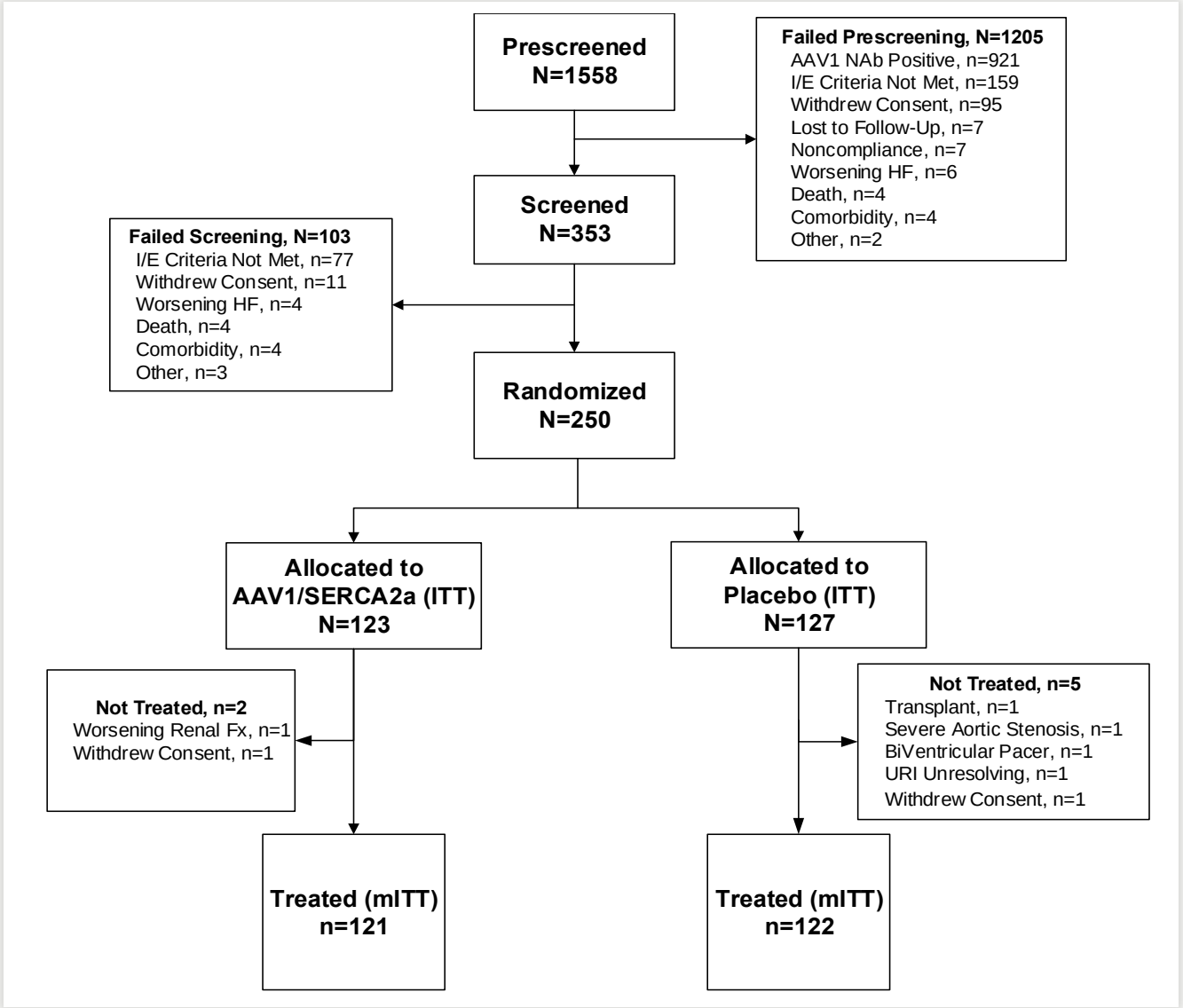
Greenberg B, Yaroshinsky A, Zsebo KM, et al. J Am Coll Cardiol HF 2014;2:84.92

CUPID 2 Study Design



RESULTS

Patient Population Flowchart



Baseline Characteristics

Characteristic	Placebo N=122	AAV1/SERCA2a N=121
Age (years), Mean (SD)	58.4 (12.26)	60.3 (9.77)
Sex, Male, n (%)	98 (80.3)	100 (82.6)
Race, White, n (%)	99 (81.1)	99 (81.8)
CAD, n (%)	67 (54.9)	68 (56.2)
6MWT (m), Mean (SD)	336.6 (71.29)	319.9 (91.47)
LVEF (%), Mean (SD)	24.0 (6.26)	23.0 (6.48)
NYHA Class, n (%)		
II	21 (17.2)	22 (18.2)
III	100 (82.0)	96 (79.3)
IV	1 (0.8)	3 (2.5)
KCCQ, Overall Score, Mean (SD)	59.2 (22.27)	58.4 (19.76)
NT-proBNP (pg.mL), Median (IQR)	1504 (849, 3031)	1754 (843.3, 3785)

Baseline Characteristics

Characteristic	Placebo N=122	AAV1/SERCA2a N=121
HF Etiology, n (%)		
Ischemic	63 (51.6)	62 (51.2)
Non-Ischemic	59 (48.4)	59 (48.8)
HF Optimized Regimen, n (%)		
ACE/ARB	110 (90.2)	111 (91.7)
Aldosterone Antagonist	74 (60.7)	83 (68.6)
Beta Blocker	117 (95.9)	117 (96.7)
Diuretic	109 (89.3)	111 (91.7)
Digoxin	48 (39.3)	45 (37.2)
OAC/NOAC*	81 (66.4)	76 (62.8)
CRT, n (%)	39 (32)	53 (43.8)
ICD, n (%)	89 (73)	98 (81)
Diabetes Type 2, n (%)	49 (40.2)	59 (48.8)

*OAC/NOAC, oral anticoagulants/novel oral anticoagulants

CUPID 2: Primary Efficacy Endpoint Results

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Of the 232 recurrent events that qualified as primary endpoints, 128 were in the placebo group and 104 were in the AAV1/SERCA2a group

Treatment with AAV1/SERCA2a failed to improve the rate of recurrent events (HR, 0·93; 95% confidence interval [CI] 0·53 to 1·65; p=0·81)

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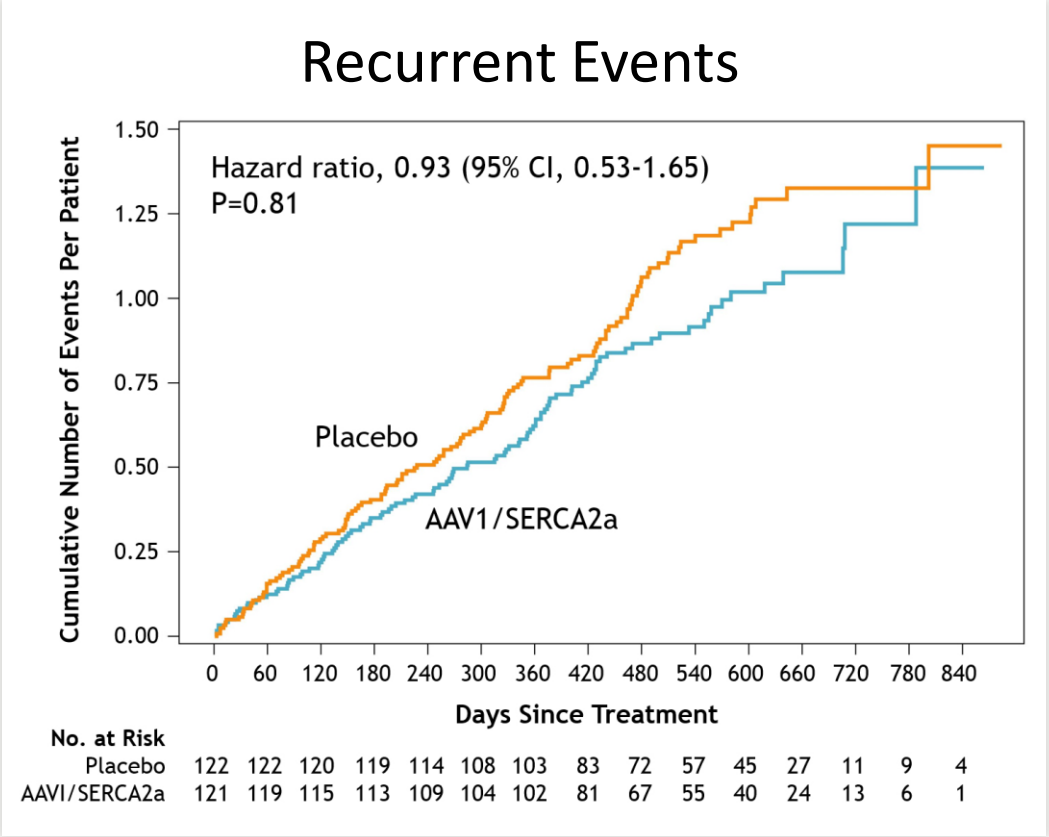
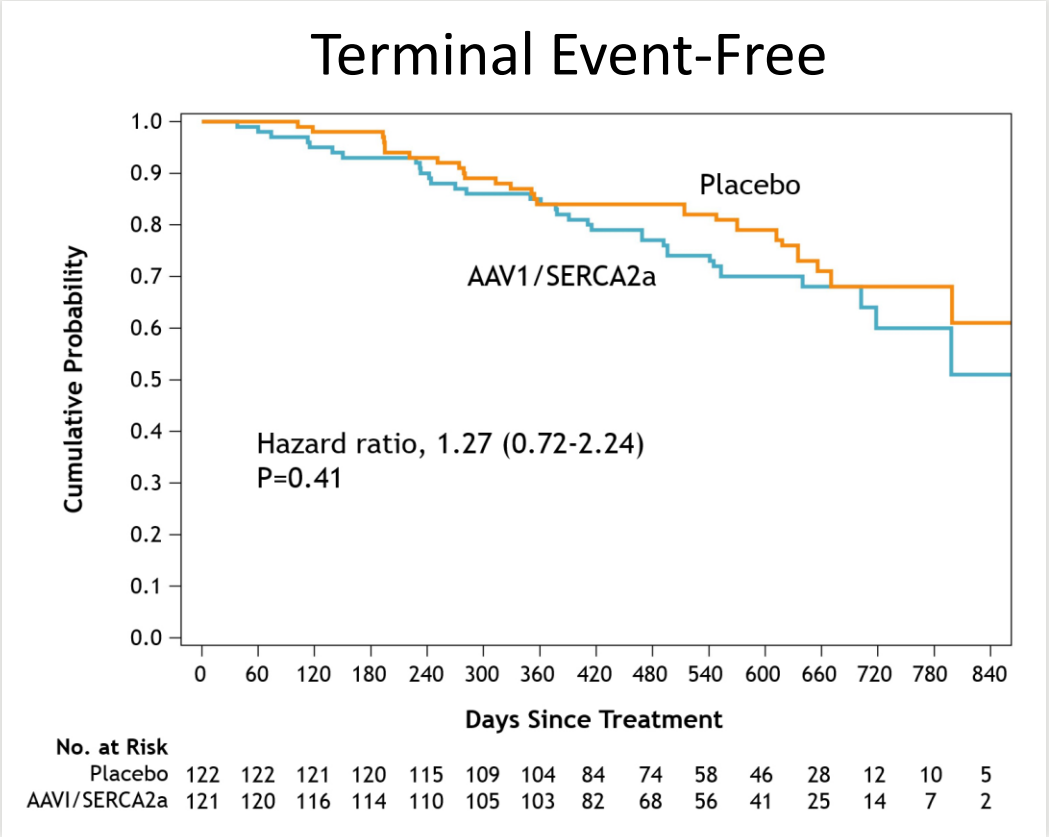


CUPID 2: Secondary Efficacy Endpoint Results

Of the 65 terminal events that qualified as secondary endpoints, 29 were in the placebo group and 36 were in the AAV1/SERCA2a group

Treatment with AAV1/SERCA2a failed to improve time to first terminal event (HR, 1·27; 95% CI 0·72 to 2·24; p=0·40)



Subgroup Analysis for Primary and Secondary Endpoints

Subgroup	# Subjects		Recurrent Events HR (95% CI)	P value	Terminal Events HR (95% CI)	P value
	Placebo	AAVI/ SERCA2a				
Overall						
ITT	127	123	0.92 (0.53, 1.62)	----	1.23 (0.71, 2.14)	----
mITT	122	121	0.93 (0.53, 1.65)		1.27 (0.72, 2.24)	
Geography						
US	79	79	0.86 (0.42, 1.77)	0.72	0.81 (0.39, 1.67)	0.02
Ex-US	43	42	1.02 (0.40, 2.62)		3.25 (1.22, 8.65)	
HF Etiology						
Ischemic	63	62	1.13 (0.50, 2.57)	0.48	1.35 (0.60, 3.02)	0.79
Non-Ischemic	59	59	0.79 (0.36, 1.72)		1.22 (0.56, 2.67)	
NYHA Class						
II	21	22	0.93 (0.28, 3.14)	0.99	1.26 (0.28, 5.76)	0.95
III or IV	101	99	0.94 (0.50, 1.79)		1.30 (0.70, 2.42)	
Years of Age						
< 65	82	76	0.73 (0.36, 1.48)	0.16	1.29 (0.66, 2.52)	0.95
≥ 65	40	45	1.75 (0.65, 4.74)		1.30 (0.44, 3.81)	
Sex						
Male	98	100	1.01 (0.54, 1.89)	0.47	1.38 (0.75, 2.55)	0.43
Female	24	21	0.60 (0.16, 2.35)		0.68 (0.13, 3.49)	
Diabetic						
No	73	62	1.59 (0.69, 3.65)	0.09	2.70 (1.04, 7.04)	0.03
Yes	49	59	0.57 (0.27, 1.22)		0.69 (0.33, 1.44)	
NT-proBNP						
< Median	66	56	0.62 (0.25, 1.57)	0.33	1.21 (0.51, 2.87)	0.99
≥ Median	56	65	1.08 (0.54, 2.16)		1.26 (0.60, 2.64)	
LVEF						
< Median	53	60	0.75 (0.36, 1.55)	0.40	1.18 (0.57, 2.43)	0.95
≥ Median	69	60	1.19 (0.49, 2.85)		1.19 (0.49, 2.90)	
ICD						
No	33	23	0.39 (0.10, 1.49)	0.15	1.28 (0.28, 5.84)	0.85
Yes	89	98	1.03 (0.55, 1.93)		1.27 (0.69, 2.34)	
Risk Factors						
None	14	15	0.44 (0.07, 2.68)	0.42	0.39 (0.03, 5.43)	0.55
NT-proBNP	41	45	1.95 (0.76, 5.05)		2.55 (0.95, 6.81)	
HF Hospitalization	30	25	0.31 (0.07, 1.46)		1.08 (0.28, 4.23)	
Both	29	31	1.05 (0.50, 2.22)		1.10 (0.43, 2.84)	

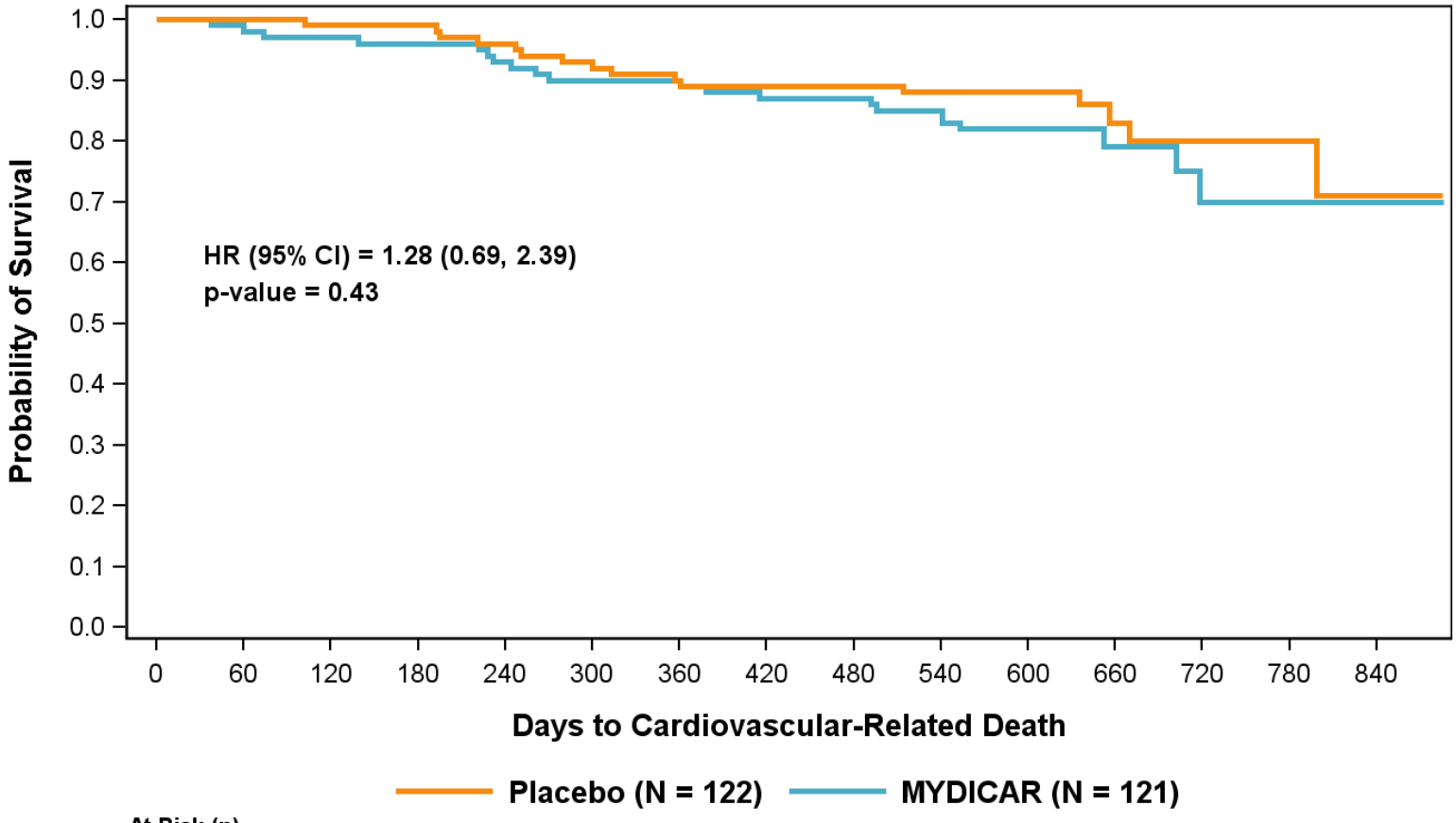
Exploratory Efficacy Endpoints

Compared to placebo, treatment with AAV1/SERCA2a had no significant effect on change from baseline in:

- NYHA Functional Class
- Percentage of patients who improved ≥ 1 NYHA Functional Class
- Distance walked over 6 minutes
- KCCQ overall score
- NT-proBNP levels

SAFETY

CV-Related Death: Safety Population



At Risk (n)															
Placebo:	122	122	122	119	118	116	113	97	79	61	52	30	20	6
MYDICAR:	121	120	117	117	113	109	109	95	73	60	50	26	19	5

*Subjects who died from other than cardiovascular-related causes were censored at their death dates.

Adjudicated Clinical Events: Safety Population

Clinical Event	Placebo (N=122) n (Rate)	AAV1/SERCA2a (N=121) n (Rate)
All clinical events	262 (147)	190 (111)
All-cause hospitalizations	240 (135)	172 (100)
HF-related hospitalizations	121 (67.9)	99 (57.7)
Ambulatory WHF	7 (4.0)	8 (4.8)
Non-fatal MI	5 (2.8)	3 (1.7)
Non-fatal stroke	3 (1.7)	5 (2.9)
Heart transplant	4 (2.2)	7 (4.1)
Durable MCSD implant	8 (4.5)	7 (4.1)
Deaths	20 (11.2)	25 (14.6)
Non-cardiovascular	2 (1.1)	3 (1.7)
Cardiovascular	18 (10.1)	22 (12.8)

Note: Rate per 100 patient-years of observation

CUPID 2: Safety

- The only treatment-emergent SAEs occurring in ≥2% of either treatment group was that placebo patients had a higher rate of ICD insertion than AAV1/SERCA2a patients (4·9% versus 0%; p=0·03)
- The only significant change in hematology, blood chemistries, cardiac enzymes, LFTs was a greater number of SERCA2a patients with BUN >ULN at 3 months (without change in creatinine or eGFR)
- No evidence of any cell-mediated immune response; a single positive ELISPOT result in a placebo patient
- No clinically meaningful changes in vital signs, ECG parameters (including QT duration), or arrhythmias on ICD interrogation
- No significant differences between study groups in change in medical therapy during the course of CUPID 2

CUPID 2: Summary

- Treatment of patients with moderate-severe heart failure with AAV1/SERCA2a did not significantly reduce the likelihood of either recurrent hospitalizations (primary end-point) or terminal events (secondary end-point)
- There was no evidence of improvement for these endpoints in any predefined or exploratory subgroup
- There were no beneficial effects on exploratory efficacy endpoints
- No safety concerns emerged

CUPID 2: Conclusions

CUPID 2 failed to support the hypothesis that AAV1/SERCA2a at the dose used has clinical benefits in patients with moderate to severe heart failure and reduced ejection fraction

What Can We Learn From the Results of CUPID 2

- Exploring questions regarding outcomes:
  - Did it turn out to be the wrong target patient population? Was the study design optimal? Were the end-points appropriate?
  - Was it the target (i.e., can we conclude that correction of SERCA2a by gene therapy doesn't improve heart failure outcomes)?
  - Was there adequate drug delivery to the cardiac myocytes? (a complex challenge with gene therapy)