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Aficamten Improves Comprehensive Measures of Exercise Performance in Non-Obstructive Hypertrophic Cardiomyopathy

A Prespecified Analysis of ACACIA-HCM

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Background

- Symptomatic nHCM remains a therapeutic challenge¹
- Aficamten is a next-in-class cardiac myosin inhibitor approved in oHCM.² It:
 - Improves exercise capacity and patient-reported health status in oHCM^{3,4}
 - Has favorable effects on diastolic function,⁵⁻⁹ a key pathophysiologic mechanism of symptoms and decreased exercise capacity in nHCM¹⁰

In the phase 3, randomized, placebo-controlled ACACIA-HCM trial, aficamten improved the primary endpoints of peak oxygen uptake and KCCQ-CSS in patients with symptomatic nHCM¹⁰

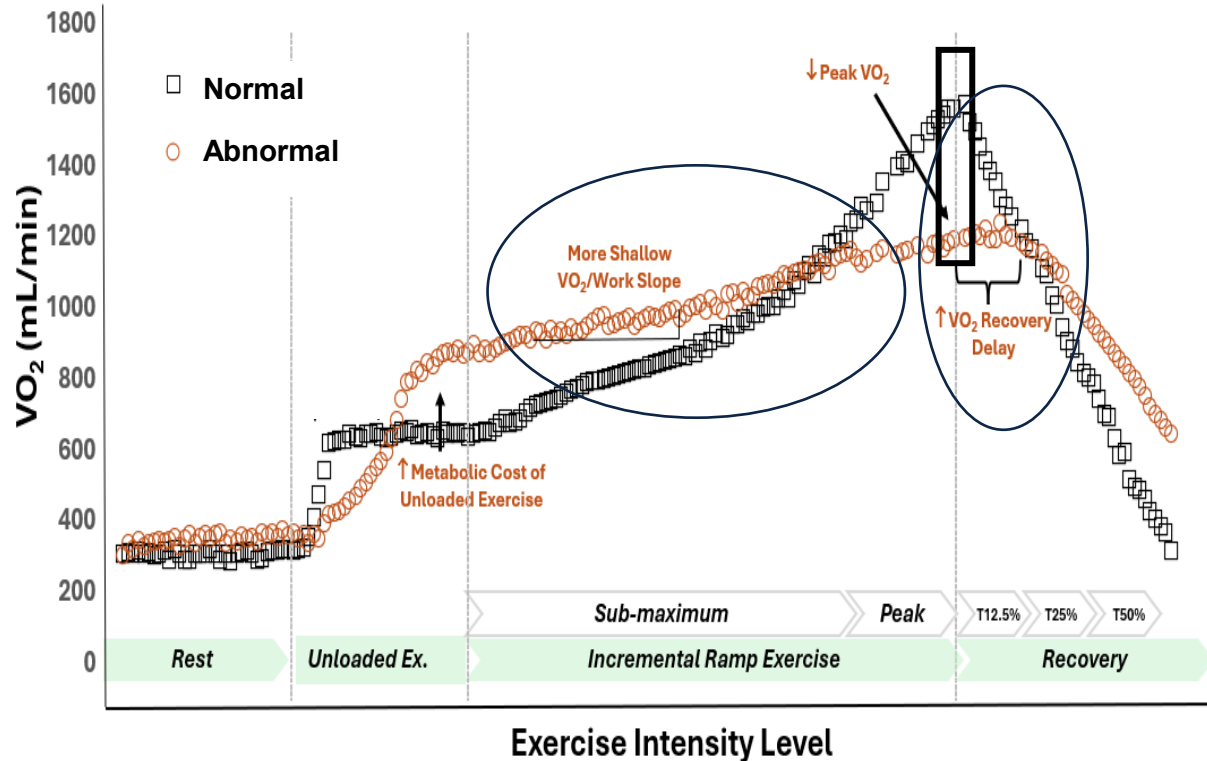
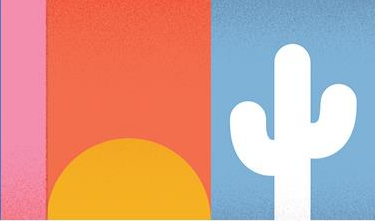
Dual primary endpoints	Change from Baseline to Week 36 LSM (95% CI)		Aficamten vs Placebo LSM (95% CI)	P-value
	Aficamten	Placebo		
KCCQ-CSS	11.4 (9.6, 13.2)	8.4 (6.6, 10.2)	3.0 (0.5, 5.5)	0.02
pVO ₂ (mL/kg/min)	0.64 (0.32, 0.95)	-0.03 (-0.35, 0.28)	0.67 (0.22, 1.11)	0.003

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LSM, least squares mean; nHCM, nonobstructive hypertrophic cardiomyopathy; oHCM, obstructive hypertrophic cardiomyopathy; pVO₂, peak oxygen uptake.

1. Ommen SR, et al. *Circulation*. 2024;149:e1239-311. 2. Myqorzo (aficamten) prescribing information. https://cytokinetics.com/wp-content/uploads/2025/12/MYQORZO_US_Prescribing_Information_and_Med_Guide.pdf. Accessed September 15, 2026. 3. Maron MS, et al. *N Engl J Med*. 2024;30:1849-61. 4. Garcia-Pavia P, et al. *N Engl J Med*. 2025;393:949-60. 5. Hedge SM, et al. *Circulation*. 2026 doi: 10.1161/CIRCULATIONAHA.126.082343. 6. Hegde SM, et al. *J Am Coll Cardiol*. 2024;84:1789-802. 7. Hegde SM, et al. *J Am Coll Cardiol*. 2025;86:2452-67. 8. Masri A, et al. *J Card Fail* 2024;30:1439-448. 9. Masri A, et al. *N Engl J Med*. 2026 Aug 28. doi: 10.1056/NEJMoa2603021. 10. Kawana M, et al. *Front Physiol* 2022;13:9750767.



Background: Exercise Responses Beyond Peak VO₂



- Multiple exercise measures complement peak VO₂ and reflect the ability to adapt to all phases of exercise
 - Submaximum exercise capacity (anaerobic threshold)
 - Breathing/Ventilatory efficiency (most and integrated)
 - Exercise duration/workload
 - Resilience: exercise recovery
 - Aerobic efficiency (VO₂/work)
 - Heart rate response to exercise
 - Blood pressure response to exercise
 - Circulatory power
 - Ventilatory power

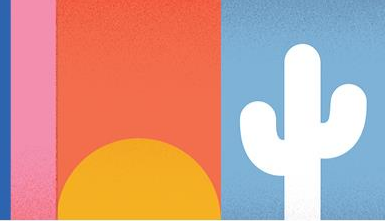
1. Masri A, et al. 2026. Aug 28. *N Engl J Med*. doi: 10.1056/NEJMoa2603021.

-Effects of aficamten on these individual exercise measures are unknown

-Whether changes in these exercise measures differ from each other in relative magnitude & direction is also unknown

Goal: Holistically understand the “net effect” of aficamten on clinically meaningful exercise response patterns

Background: ©2026 Boston Exercise Aggregate Physiologic Response Score (BEAP-RS)



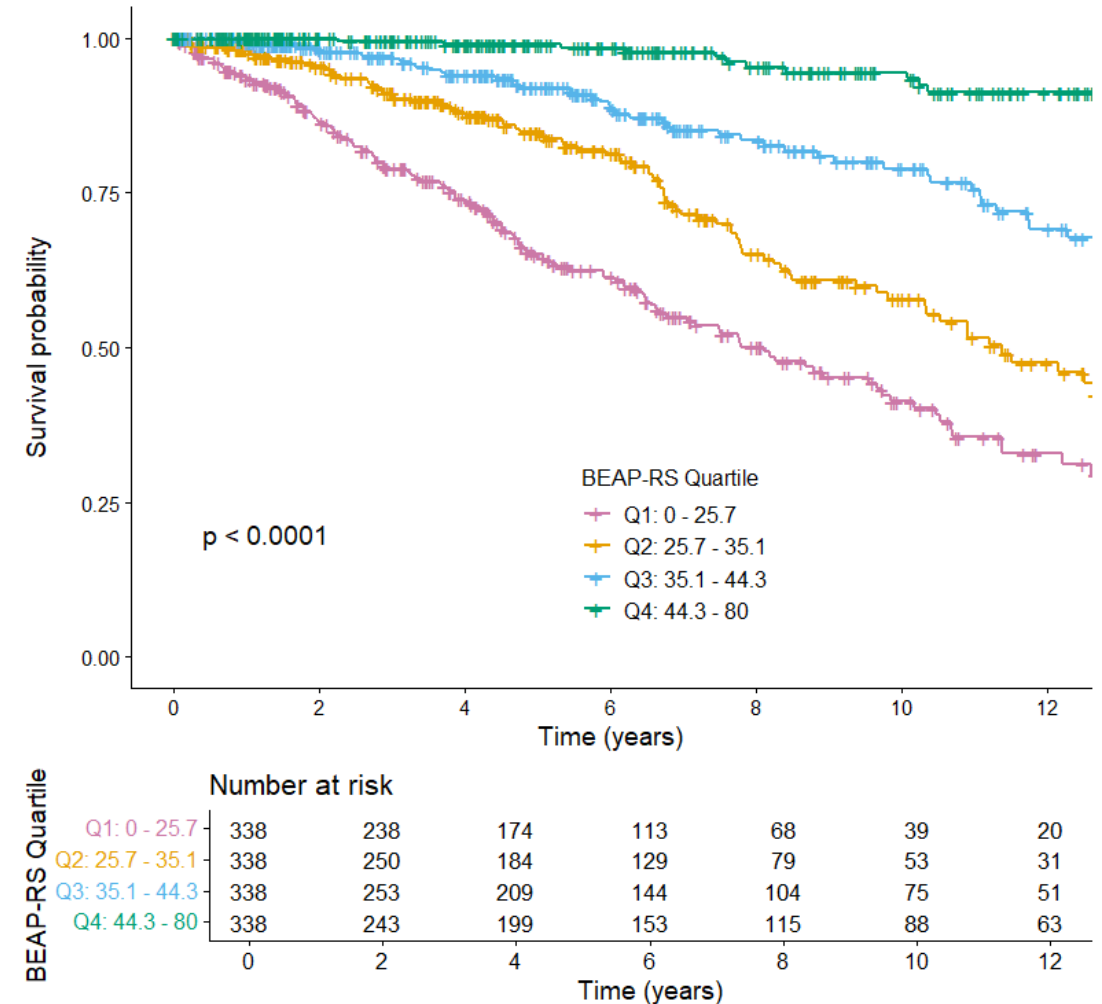
Submax VO ₂ AT	Peak VO ₂	Recovery VO ₂ kinetics
VE/VCO ₂ relationship	Workload achieved	

5 domains → score range of 0-80

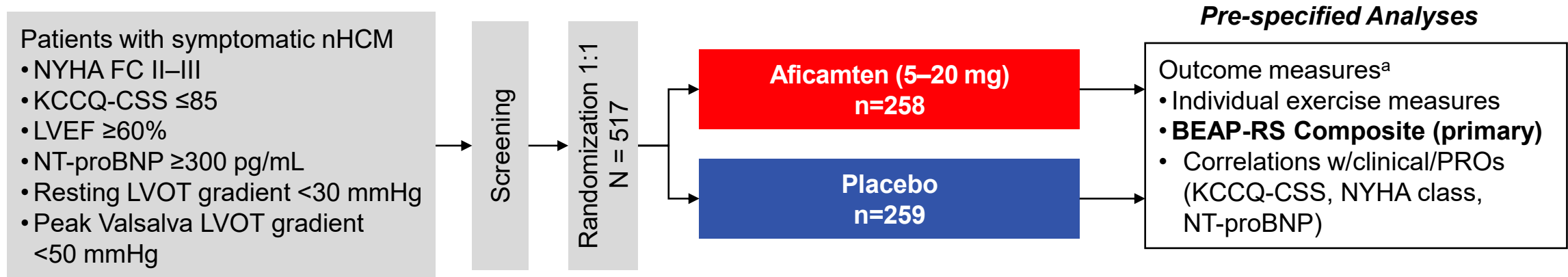
Pre-specified bin width (points) correspond to a clinically meaningful change in each variable

N=1,352, age 61±14, 51% female, BMI 30±6
Combined MGH referral cohort of HF, PH, HCM

After adjustment for age, sex, BMI each 1-point increment in BEAP-RS was associated with 6.2% lower mortality (HR 0.94, [CI 0.93, 0.95], p<0.0001)



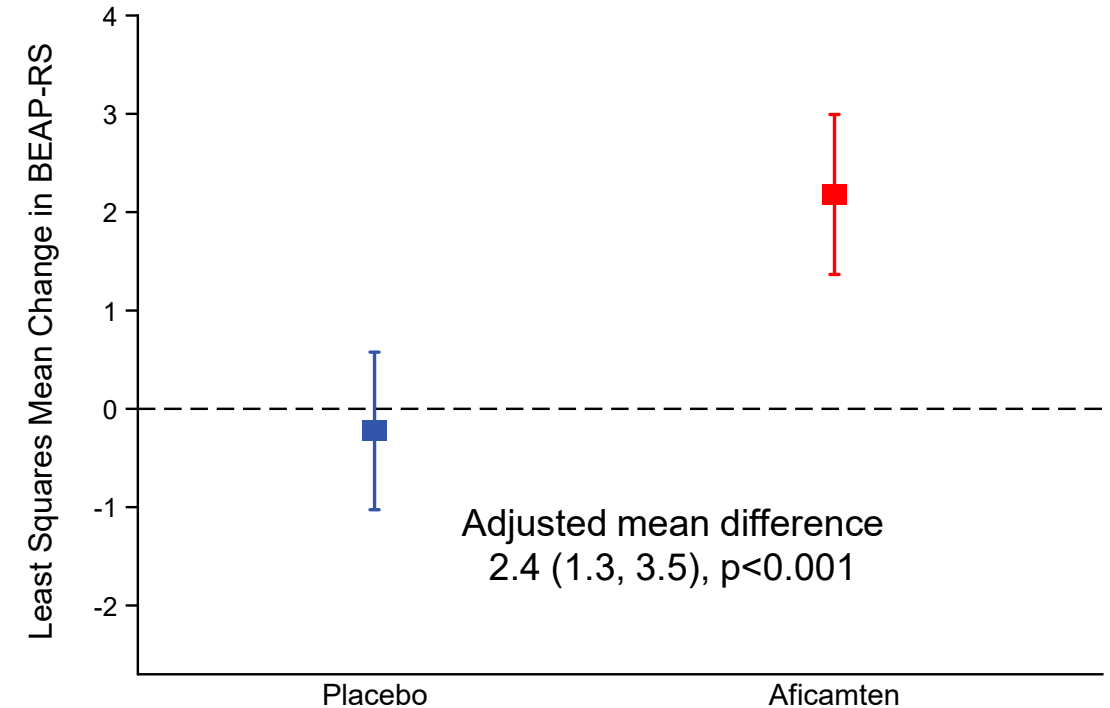
Objectives and Methods



- We hypothesized that aficamten improves multiple exercise parameters in nHCM that are uniquely captured within the novel **©2026 Boston Exercise Aggregate Physiologic Response Score (BEAP-RS)**

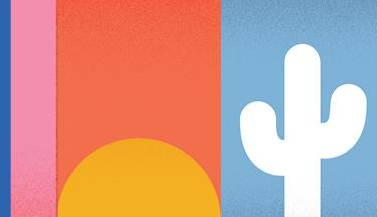
Results: Changes in BEAP-RS at Week 36

- Mean ($\pm$ SD) age of participants was 55.1 ± 16.1 years, 240 (46.4%) were men, and 473 (91.5%) had core-laboratory validated exercise tests both at baseline and Week 36.
- Compared with placebo, aficamten treatment improved the novel BEAP-RS score at Week 36.



BEAP-RS							
Baseline Aficamten	Week 36 Aficamten	Absolute difference (SD) ^a	Baseline Placebo	Week 36 Placebo	Absolute difference (SD) ^a	Between group difference (95% CI) ^b	p-value
40.2 $\pm$ 13.6	42.4 $\pm$ 13.8	2.2 $\pm$ 7.0	40.7 $\pm$ 12.4	40.4 $\pm$ 12.2	-0.3 $\pm$ 5.9	2.4 (1.3, 3.5)	$p < 0.001$

Results: Changes in Individual Exercise Response Variables at Week 36



Variable	Baseline Aficamten	Week 36 Aficamten	Absolute difference (SD) ^a	Baseline Placebo	Week 36 Placebo	Absolute difference (SD) ^a	Between group difference (95% CI) ^b	p-value
SUBMAXIMUM EXERCISE CAPACITY								
Anaerobic Threshold (mL)	865 ± 259	884 ± 265	19 ± 117	858 ± 257	854 ± 247	-4 ± 105	24 (4, 44)	p= 0.016
Aerobic Efficiency (mL/min/watt)	8.8 ± 2.5	9.0 ± 2.5	0.2 ± 2.0	8.9 ± 2.2	8.6 ± 2.2	-0.3 ± 1.7	0.4 (0.1, 0.7)	p= 0.012
VENTILATORY EFFICIENCY								
Ventilatory Efficiency	34.9 ± 8.0	33.9 ± 7.3	-1.0 ± 5.3	34.1 ± 6.4	34.3 ± 5.6	0.2 ± 4.2	-1.0 (-1.7, -0.2)	p= 0.014
VE/VCO ₂ - Nadir	32.2 ± 5.3	31.7 ± 5.0	-0.5 ± 2.9	32.1 ± 4.6	32.4 ± 4.5	0.2 ± 2.8	-0.7 (-1.2, -0.2)	p= 0.003
PEAK EXERCISE								
pVO ₂ per Kg (mL/kg/min)	18.1 ± 5.3	18.8 ± 5.8	0.6 ± 2.6	18.1 ± 5.1	18.1 ± 5.5	0 ± 2.4	0.7 (0.2, 1.1)	p= 0.004
Workload (Watt)	107 ± 41	110 ± 42	3 ± 16	108 ± 38	108 ± 40	0 ± 16	3 (1, 6)	p= 0.020
Peak Heart Rate (beats/min)	130 ± 25	135 ± 25	5 ± 14	130 ± 24	130 ± 26	0 ± 15	5 (2, 7)	p<0.001
Peak SBP (mmHg)	157 ± 31	160 ± 32	2 ± 26	156 ± 28	154 ± 27	-2 ± 23	5 (1, 9)	p= 0.025
POST-EXERCISE RECOVERY								
Recovery Delay (s)	23 ± 23	24 ± 22	1 ± 23	25 ± 22	26 ± 21	1 ± 25	-1 (-4, 3)	p= 0.69
VO ₂ recovery 12.5% (s)	45 ± 23	42 ± 22	-3 ± 19	43 ± 21	44 ± 21	1 ± 18	-3 (-6, -0)	p= 0.027
2-COMPONENT COMPOSITE VARIABLES								
Circulatory Power ^a (mmHg*mL/min/kg)	2879 ± 1144	3008 ± 1212	129 ± 637	2803 ± 922	2783 ± 1041	-20 ± 612	154 (41, 268)	p= 0.008
Ventilatory Power ^b mmHg	4.7 ± 1.3	4.9 ± 1.5	0.20 ± 0.95	4.7 ± 1.2	4.6 ± 1.2	-0.10 ± 0.90	0.31 (0.14, 0.47)	p<0.001

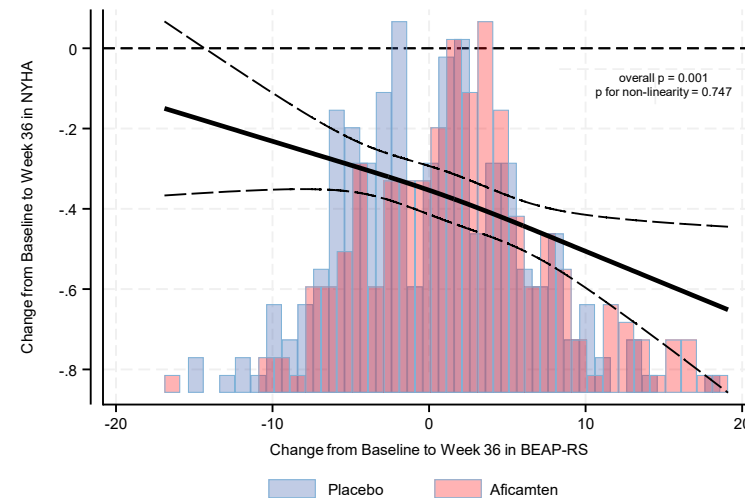
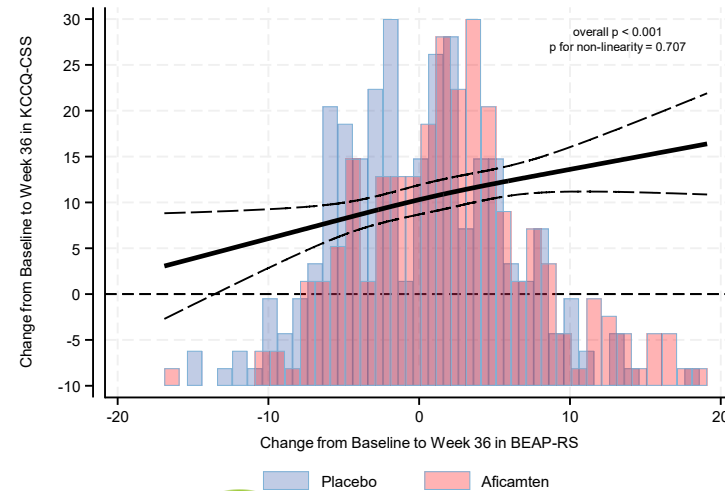
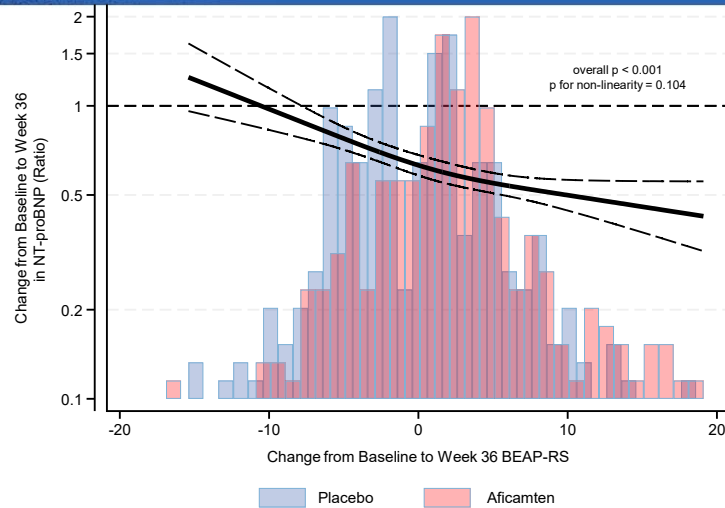
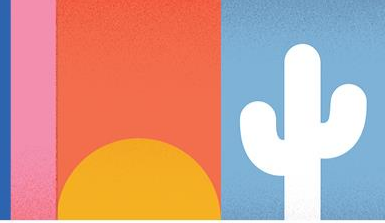
Aficamten improved exercise and recovery measures across all 5 BEAP-RS domains



Data are shown as mean ± SD unless otherwise specified. ^aCirculatory power is derived from the product of peak systolic BP and pVO₂.

^bVentilatory power is derived from the product of VE/VCO₂ slope divided by SBP. BEAP-RS, Boston Exercise Aggregate Physiologic Response Score; pVO₂, peak oxygen uptake; SBP, systolic blood pressure; VCO₂, carbon dioxide output; VE, minute ventilation; VO₂, oxygen uptake.

Results: Correlation of BEAP-RS with Clinical and PROs



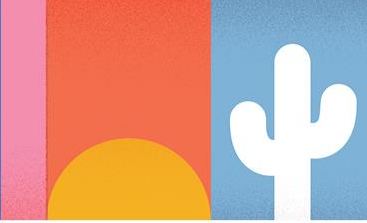
KCCQ	0.08	0.12	-0.16	0.14	0.12	0.11	-0.01	0.18
NYHA	-0.11	-0.07	0.14	-0.15	-0.15	-0.10	-0.01	-0.19
LAVI	0.01	-0.05	0.13	0.01	0.04	-0.07	0.08	0.01
lateral E/e'	-0.05	-0.09	0.13	-0.11	-0.16	-0.15	0.12	-0.18
Log-transformed NTproBNP	-0.17	-0.18	0.23	-0.19	-0.13	-0.19	0.14	-0.27
Log-transformed Troponin	-0.09	-0.08	0.10	-0.12	-0.05	-0.09	0.10	-0.14
	VO2 AT	VO2/work	VE/VO2 slope	Peak VO2	Peak Work	Peak HR	VO2 T12.5	

BEAP CPET composite score
All $p < 0.005$ and Highest
CPET Variable Correlate

Conclusions

- In this prespecified analysis of ACACIA-HCM, aficamten consistently improved a broad range of exercise response patterns in nHCM at week 36
 - The novel, integrated ©BEAP-RS improved by +2.4 points w/aficamten vs. placebo
 - This effect size would translate to a ~15% survival improvement in a distinct derivation cohort
 - Improvements correlated with improvements in KCCQ-CSS, NYHA functional class, diastolic function (E/e'), and NT-proBNP levels
- Future studies will evaluate holistic assessment of exercise responses with ©BEAP-RS for risk stratification, trial entry criteria, and capturing net effects of interventions on exercise capacity

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