

Supplementary Online Content

Lee MMY, Masri A, Nassif ME, et al; SEQUOIA-HCM Investigators. Aficamten and cardiopulmonary exercise test performance: a substudy of the SEQUOIA-HCM randomized clinical trial. *JAMA Cardiol*. Published online September 4, 2024. doi:10.1001/jamacardio.2024.2781

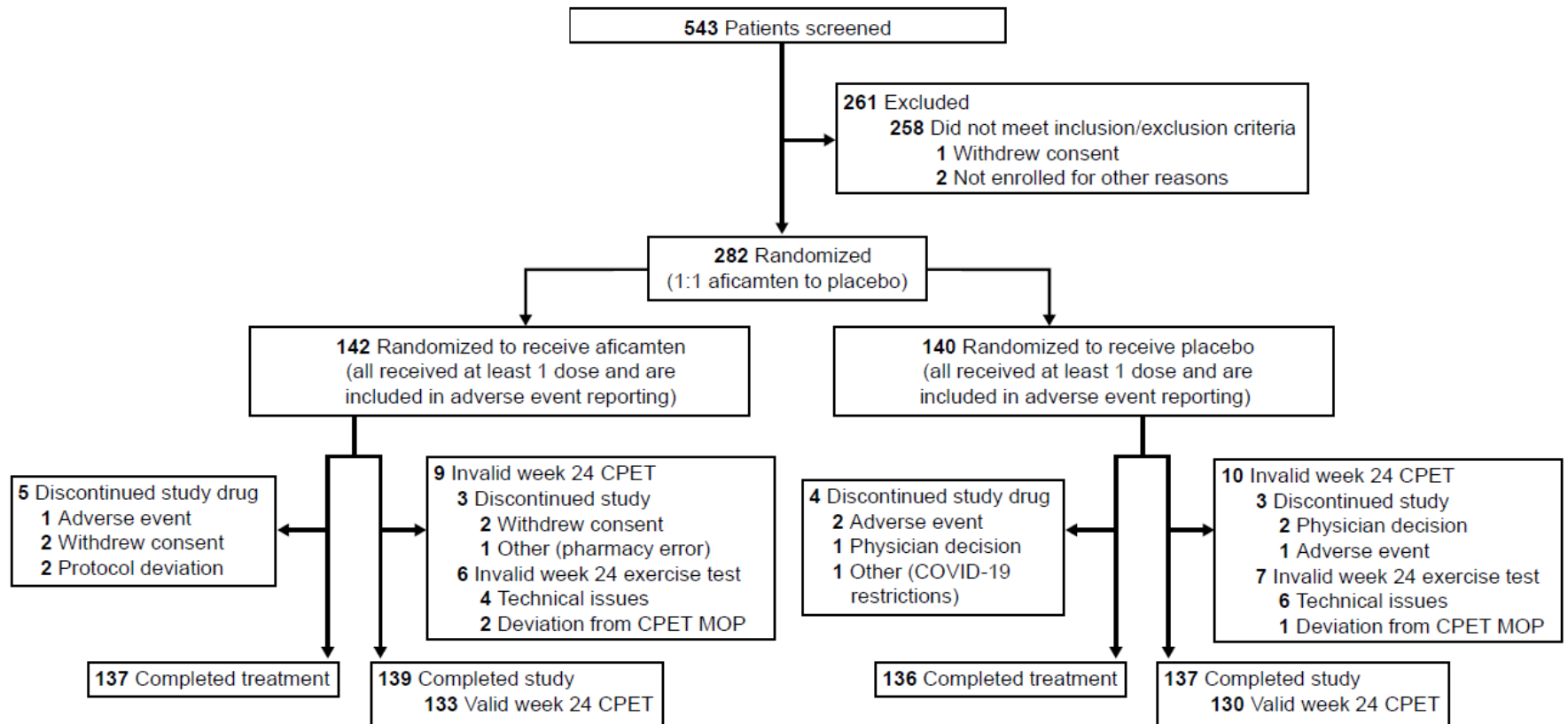
eFigure. CONSORT Diagram: Recruitment, Randomization, and Follow-Up in the SEQUOIA-HCM Trial

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eFigure. CONSORT Diagram: Recruitment, Randomization, and Follow-up in the SEQUOIA-HCM Trial



COVID-19 indicates coronavirus disease 2019; CPET, cardiopulmonary exercise test; MOP, manual of operations; SEQUOIA-HCM, Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM.

eTable 1. Responder Analyses of Categorical Change in pVO₂ With Aficamten vs Placebo at 24 Weeks

Outcome	Placebo	Aficamten	OR (95% CI)	Risk difference (95% CI)	NNT
Any improvement (small/moderate/large)	67 (47.9%)	105 (73.9%)	3.09 (1.88 to 5.09)	+26% (+15% to +37%)	3.8
Moderate/large improvement	44 (31.4%)	75 (52.8%)	2.44 (1.50 to 3.96)	+21% (+10% to +33%)	4.7
Large improvement	23 (16.4%)	46 (32.4%)	2.44 (1.38 to 4.29)	+15% (+6% to +26%)	6.3
Any deterioration (small/moderate/large)	73 (52.1%)	37 (26.1%)	0.32 (0.20 to 0.53)	-26% (-37% to -15%)	-3.8

NNT indicates number needed to treat; OR, odds ratio; pVO₂, peak oxygen uptake.

eTable 2. Univariate Correlations Between Change in Components of Integrated Exercise Response z Score and Changes in Other Measures

		Overall		
		N	Correlation	P value
Change in <u>pVO₂</u> vs	Clinical variable			
	KCCQ-CSS	262	0.206	< .001
	NYHA functional class	263	-0.173	= 0.005
	Log-transformed NT-proBNP	254	-0.328	< .001
	Log-transformed hs-cTnl	246	-0.141	= 0.03
	Resting LVOT-G	258	-0.162	= 0.009
	Valsalva LVOT-G	258	-0.135	= 0.03
	LAVI	253	-0.094	= 0.14
	Septal E/e'	251	-0.244	< .001
	Mitral regurgitation	255	-0.104	= 0.10
	Exercise test variable			
	Workload	262	0.517	< .001
	Exercise duration	243	0.518	< .001
	Peak RER	263	0.000	> .99
	Peak systolic blood pressure	252	0.290	< .001
	Ventilatory efficiency throughout exercise	263	-0.227	< .001
	Ventilatory efficiency pre-anaerobic threshold	262	-0.285	< .001
Anaerobic threshold	262	0.750	< .001	
Change in <u>VE/VCO₂ slope throughout exercise</u> vs	Clinical variable			
	KCCQ-CSS	264	-0.158	= 0.010
	NYHA functional class	265	0.284	< .001
	Log-transformed NT-proBNP	256	0.312	< .001
	Log-transformed hs-cTnl	248	0.074	= 0.24
	Resting LVOT-G	260	0.244	< .001
	Valsalva LVOT-G	260	0.222	< .001
	LAVI	255	0.136	= 0.03
	Septal E/e'	253	0.105	= 0.09
Mitral regurgitation	257	-0.103	= 0.10	

Exercise variable

Workload	263	-0.050	= 0.42
Exercise duration	244	-0.097	= 0.13
Peak RER	265	-0.035	= 0.57
Peak systolic blood pressure	254	-0.079	= 0.21
Ventilatory efficiency throughout exercise	265	1.000	< .001
Ventilatory efficiency pre-anaerobic threshold	264	0.505	< .001
Anaerobic threshold	262	-0.234	< .001

Abbreviations: hs-cTnl, high-sensitivity cardiac troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LAVI, left atrial volume index; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; pVO₂, peak oxygen uptake; RER, respiratory exchange ratio; VCO₂, carbon dioxide output; VE, minute ventilation.

eTable 3. Multivariate Regression Model to Evaluate Independent Degree of Variance Explained in Change in pVO₂ and VE/VCO₂ Slope From Baseline to Week 24 by Clinical Variables

	Multivariate regression model covariates	R ²	Change in R ²
Variance explained in change in <u>pVO₂</u>	1) pVO ₂	0.037	N/A
	2) model 1 + log-transformed NT-proBNP	0.200	0.163 ^a
	3) model 2 + E/e'	0.215	0.015 ^a
	4) model 3 + KCCQ-CSS	0.239	0.024 ^a
	5) model 4 + NYHA class	0.253	0.014
	6) model 5 + resting LVOT-G	0.260	0.007
	7) model 6 + log-transformed hs-cTnI	0.269	0.009
	8) model 7 + Valsalva LVOT-G	0.283	0.014
	9) model 8 + mitral regurgitation	0.290	0.008
	10) model 9 + LAVI	0.309	0.019
Variance explained in change in <u>VE/VCO₂</u> slope throughout exercise	1) VE/VCO ₂ throughout exercise	0.094	N/A
	2) model 1 + log-transformed NT-proBNP	0.167	0.073 ^a
	3) model 2 + NYHA class	0.181	0.014
	4) model 3 + LVOT-G rest	0.197	0.016
	5) model 4 + LVOT-G Valsalva	0.200	0.003
	6) model 5 + KCCQ-CSS	0.201	0.002
	7) model 6 + LAVI	0.224	0.023 ^a
	8) model 7 + E/e'	0.237	0.012
	9) model 8 + mitral regurgitation	0.273	0.036 ^a

Abbreviations: hs-cTnI, high-sensitivity cardiac troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LAVI, left atrial volume index; LVOT-G, left ventricular outflow tract gradient; N/A, not available; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; pVO₂, peak oxygen uptake; VCO₂, carbon dioxide output; VE, minute ventilation.

^a Indicates a significance level with $P < .05$ for incremental variance explained in change in pVO₂ or change in VE/VCO₂ slope throughout exercise from baseline to week 24.