Effect of Aficamten on Cardiac Structure and Function in Patients with Obstructive Hypertrophic Cardiomyopathy: The SEQUOIA-HCM CMR Trial

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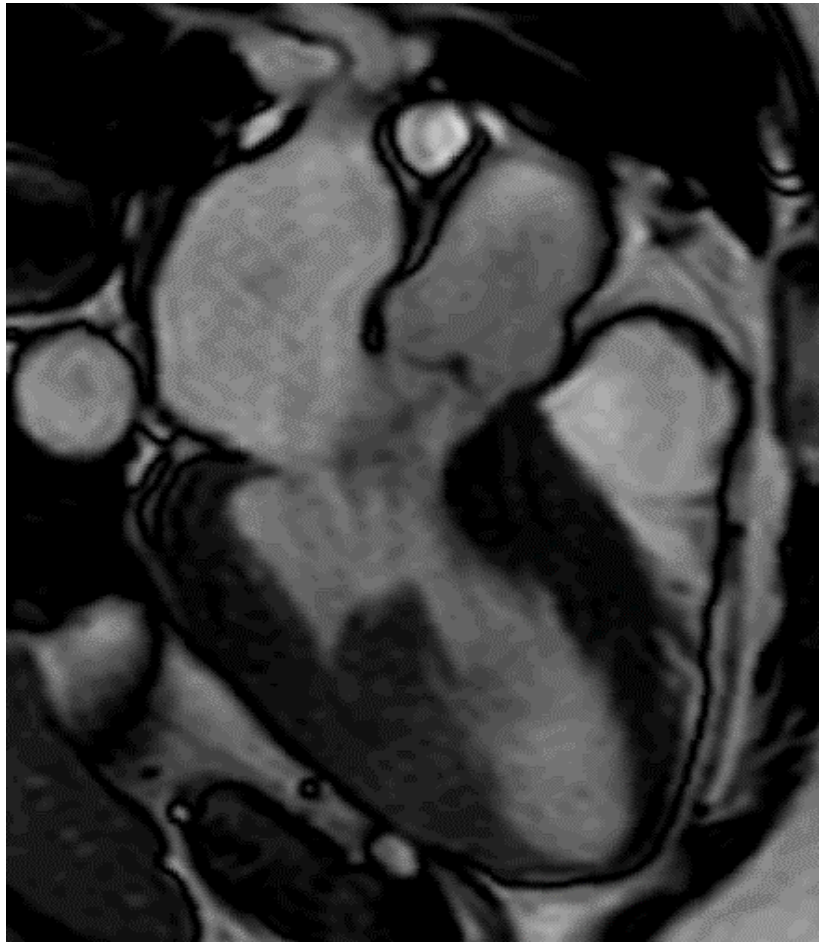
Background

- Hypercontractility due to excessive myosin-actin interaction increases LV pressure and leads to progressive LV hypertrophy and adverse cardiac remodeling.
  - This remodeling is a fundamental mechanism responsible for LVOT obstruction and oHCM.

- Aficamten is a next-in-class CMI in development for the treatment of oHCM and reduces hypercontractility in the cardiac sarcomere.

- CMR enables the detailed evaluation of myocardial structure and function and provides the most precise means for evaluating therapeutic response.

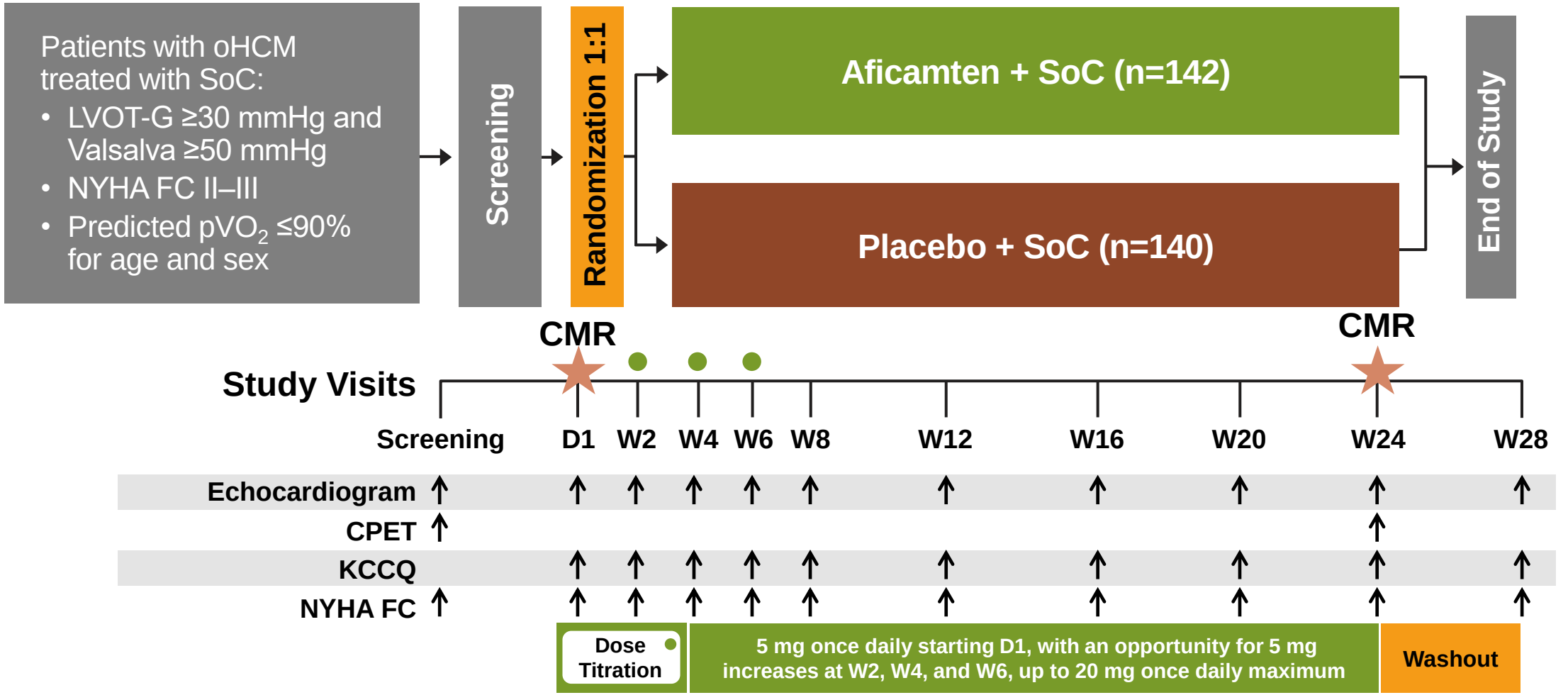


CMI, cardiac myosin inhibitor; CMR, cardiac magnetic resonance; LV, left ventricular; LVOT, left ventricular outflow tract; oHCM, obstructive hypertrophic cardiomyopathy

Purpose

- To investigate the effect of aficamten compared with placebo on cardiac structure and function by cardiovascular magnetic resonance (CMR) and link these changes with key clinical endpoints in the SEQUOIA-HCM CMR Substudy (NCT05186818).

Methods: SEQUOIA-HCM Study Design



CPET, cardiopulmonary exercise testing; D, day; IP, investigational product; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA FC, New York Heart Association functional class; pVO_2, peak oxygen uptake; SoC, standard of care; W, week.

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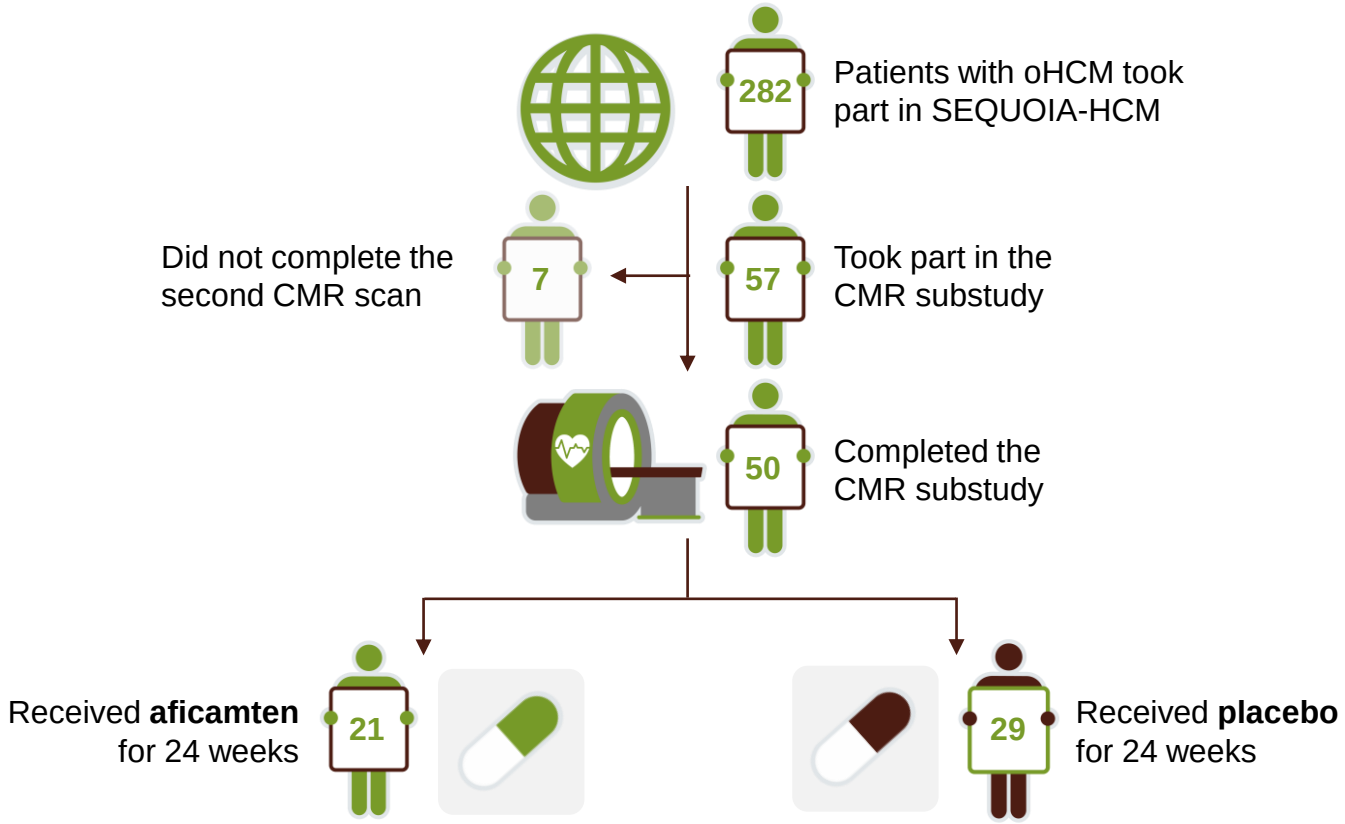
Methods: SEQUOIA-HCM CMR Trial



- **Primary endpoint:** Change from baseline in LVMI
- **Secondary endpoints:** Change from baseline in: LV wall thickness, LAV index (LAVI); LV end-diastolic volume index, LV end-systolic volume index, mitral regurgitation volume and fraction, LGE mass (6SD method), % LGE mass; ECV

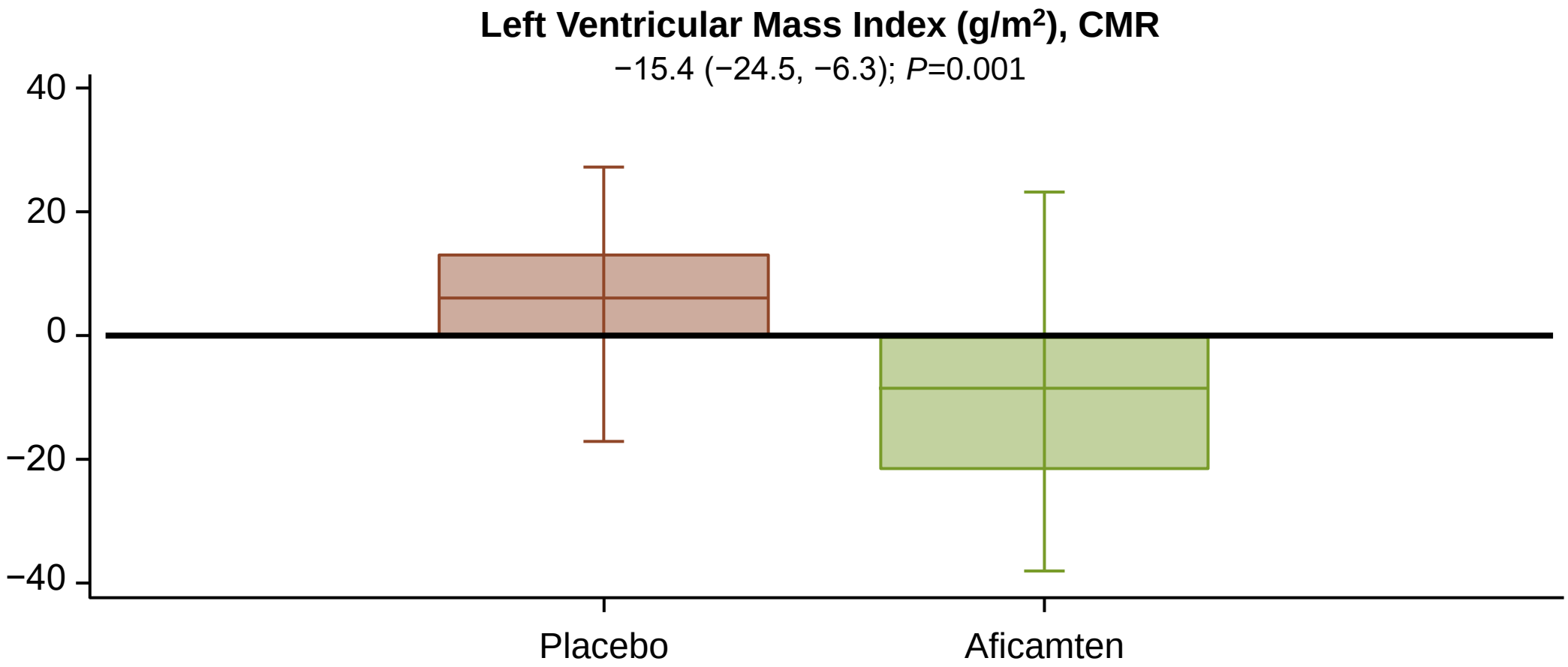
6SD, 6 standard deviation method; ECV, extracellular volume; LAVI, left atrial volume index; LGE, late gadolinium enhancement; LVMI, left ventricular mass index

Results: Baseline Characteristics

Characteristic	Non-CMR Cohort n=225	CMR Cohort n=57
Age, y	59.3 ± 13.5	58.5 ± 10.8
Female sex, n (%)	95 (42.2)	20 (35.1)
Non-White race , n (%)	55 (24.4)	4 (7.1)
Known HCM-causing gene mutation, n (%)	41 (18.2)	8 (14.0)
Positive family history of HCM, n (%)	60 (26.7)	15 (26.3)
Time since diagnosis, median (IQR), y	4.0 (1.4, 9.0)	4.4 (1.4, 6.7)
Beta-blocker, n (%)	138 (61.3)	35 (61.4)
Non-dihydropyridine calcium channel blocker	65 (28.9)	16 (28.1)
Disopyramide	31 (13.8)	5 (8.8)
History of atrial fibrillation, n (%)	37 (16.4)	7 (12.3)
NYHA FC ≥ III, n (%)	50 (22.2)	18 (31.6)
NT-proBNP, median (IQR), pg/mL	808 (346–1828)	655 (358–1146)
Cardiopulmonary exercise testing % predicted pVO_2, % pVO_2, mL/kg/min	 56.2 ± 12.1 18.2 ± 4.5	 59.4 ± 10.5 19.5 ± 4.2

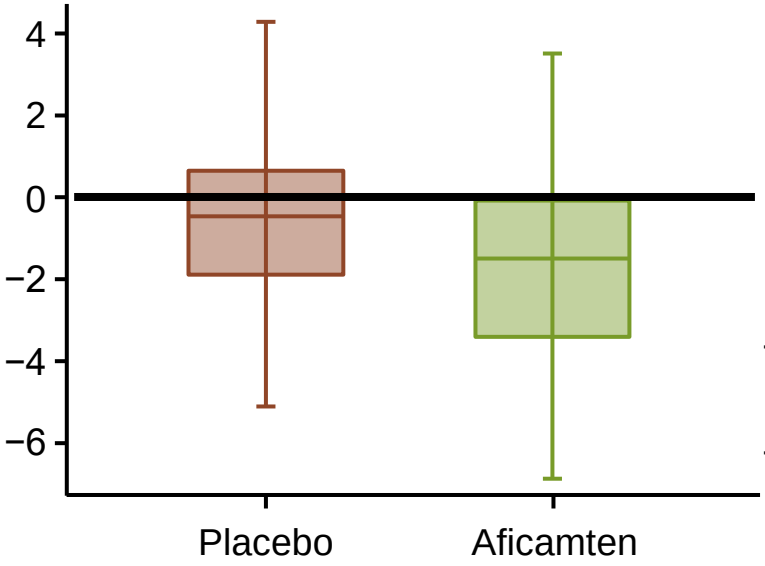
IQR, interquartile range; NT-proBNP, N-terminal pro B-type peptide

Primary Endpoint: Change in LVMI from Baseline to Week 24

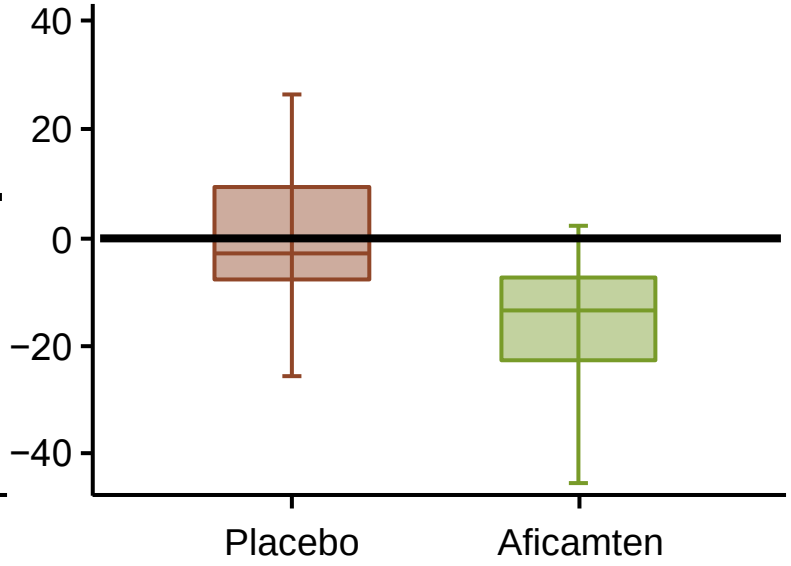


Change in LV Wall Thickness, LAVI, and Native T1

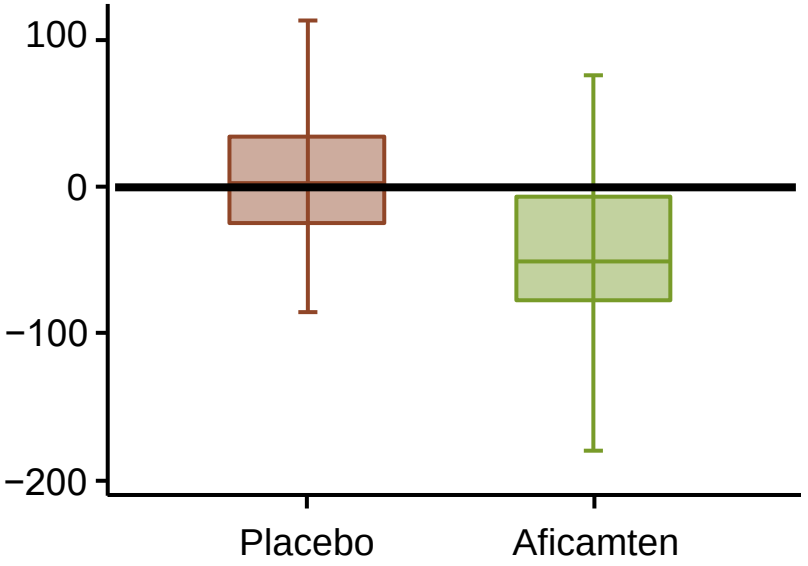
Maximal wall thickness (mm)
−1.2 (−1.8, −0.6); *P*<0.001



LA volume maximum index (mL/m²), CMR
−12.8 (−19.0, −6.7); *P*<0.001



Global Native T1 (ms), CMR
−36.8 (−68.8, −4.7); *P*=0.026



BL, baseline; LA, left atrial

Results: Changes in CMR – Cardiac Structure and Function from Baseline to Week 24

Endpoint	Aficamten n=21		Placebo n=29		Treatment Effect (95% CI)	*P* value
	Baseline	Week 24	Baseline	Week 24		
LV ejection fraction, %	77.4 ± 5.6	73.8 ± 5.9	79.0 ± 5.6	77.3 ± 7.2	−2.6 (−5.9, 0.7)	0.12
LV end diastolic volume index, mL/m²	67 ± 15	60 ± 11	67 ± 15	61 ± 15	−1 (−6, 5)	0.79
LV end systolic volume index, mL/m²	15.3 ± 5.9	16.0 ± 5.1	14.4 ± 6.4	14.1 ± 6.8	1.4 (−1.3, 4.1)	0.30
Mitral regurgitation fraction (range), %	24 (15, 47)	13 (7, 20)	30 (18, 41)	21 (14, 26)	−6 (−16, 4)	0.22
LGE, % of LV mass (range)	2.0 (0.3, 3.8)	1.4 (0.7, 2.2)	2.5 (0.7, 7.4)	1.7 (0.6, 3.8)	−0.4 (−2.1, 1.2)	0.60
LV extracellular volume fraction, %	26.7 ± 2.7	27.4 ± 7.1	28.5 ± 4.7	28.1 ± 3.1	0.7 (−2.2, 3.6)	0.61
LV extracellular volume mass index (%/g/m²)	31 ± 10	29 ± 12	30.7 ± 9.4	33 ± 11	−3.9 (−7.0, −0.9)	0.014
Absolute myocyte mass index (g/m²)	84 ± 25	75 ± 22	77 ± 20	84 ± 23	−14 (−23, −4)	0.004

Data shown as mean ± SD unless otherwise specified

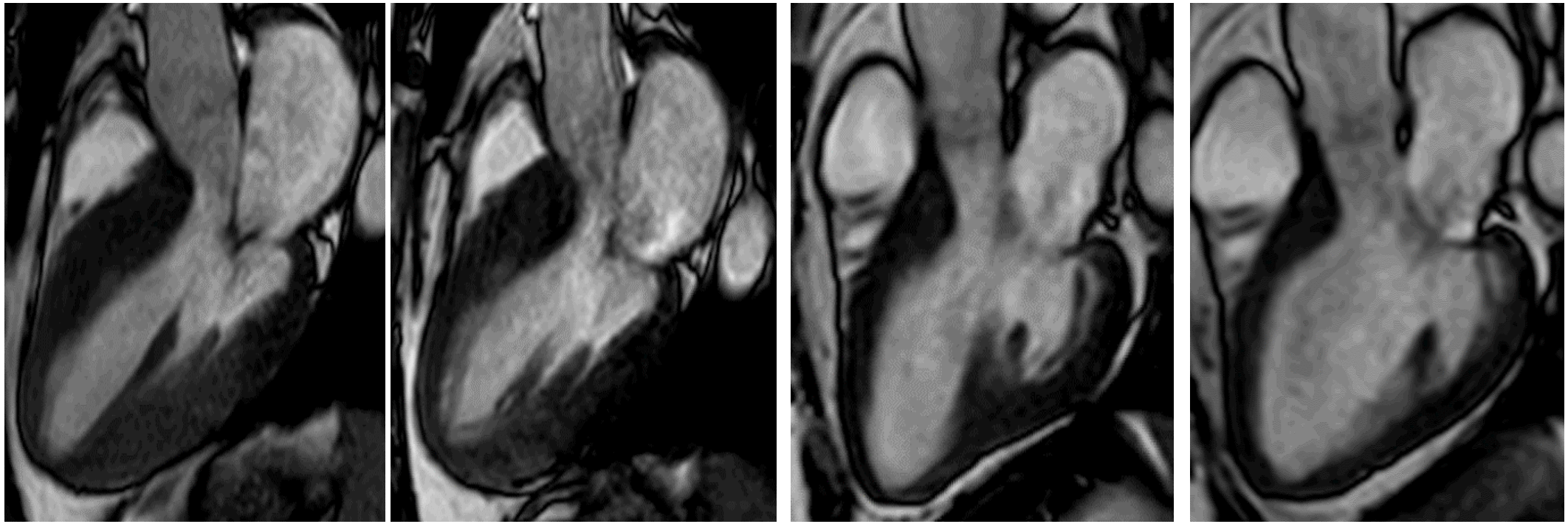
Results: Key Clinical Endpoints in the CMR Substudy

Clinical Endpoints	Aficamten n=25		Placebo n=32		Treatment Effect (95% CI)	*P* value
	Baseline	Week 24	Baseline	Week 24		
Echo LVOT gradient at rest, mmHg	55 ± 30	25 ± 25	51 ± 34	63 ± 41	−38 (−56, −20)	<0.001
Echo LVOT gradient with Valsalva, mmHg	84 ± 42	38 ± 30	84 ± 35	85 ± 40	−47 (−65, −30)	<0.001
NT-proBNP, median (IQR), pg/mL	708 (447,1160)	81 (40,207)	644 (310,1121)	594 (269,1815)	−85 (−89, −78)	<0.001
Peak oxygen consumption, pVO_2, mL/kg/min	19.8 ± 4.7	21.0 ± 4.9	19.4 ± 3.9	19.4 ± 4.1	1.2 (−0.3, 2.6)	0.11
Improvement in NYHA by ≥1 FC, n (%)	N/A	15 (60.0)	N/A	11 (34.4)	OR 3.00 (0.99, 9.10)	0.05

Data shown as mean ± SD unless otherwise specified
N/A, not applicable; OR, odds ratio

Results: Aficamten vs Placebo

Placebo		Aficamten	
Baseline	Week 24	Baseline	Week 24



Conclusions

- In the SEQUOIA-CMR Substudy, aficamten treatment for 24 weeks resulted in favorable cardiac remodeling, including reduced LV mass, LV wall thickness, and LAVI with stable interstitial and replacement fibrosis.
- The structural changes observed with CMR occurred in conjunction with similar improvements in hemodynamics, symptoms, and biomarkers.
- These data support the need for longitudinal CMR studies to assess treatment response in patients with HCM.
  - The FOREST-HCM CMR Substudy (NCT04848506) is an ongoing 5-year study that aims to assess longer-term cardiac remodeling in response to aficamten in both obstructive and non-obstructive HCM.
  - The ongoing ACACIA-HCM CMR Substudy (NCT06081894) will evaluate the effect of aficamten as compared with placebo on cardiac structure and function in patients with non-obstructive HCM.

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- Investigators and study site staff
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Effect of Aficamten on Cardiac Structure and Function in Obstructive Hypertrophic Cardiomyopathy

SEQUOIA-HCM CMR Substudy

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ABSTRACT

BACKGROUND Obstructive hypertrophic cardiomyopathy (oHCM) is characterized by left ventricular (LV) hypertrophy, LV outflow tract obstruction, and left atrial dilation, which can be associated with progressive heart failure, atrial fibrillation, and stroke. Aficamten is a next-in-class cardiac myosin inhibitor that reduces outflow tract obstruction by modulating cardiac contractility, with the potential to reverse pathological remodeling and, in turn, reduce cardiovascular events.

OBJECTIVES This study sought to investigate the effect of aficamten on cardiac remodeling compared with placebo using cardiovascular magnetic resonance (CMR) and its association with key clinical endpoints in the SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM) CMR substudy.

METHODS SEQUOIA-HCM was a phase 3 double-blind, placebo-controlled trial for adults with symptomatic oHCM who were randomized 1:1 to 24 weeks of aficamten (dose range: 5-20 mg) or placebo. Eligible participants were offered enrollment in the CMR substudy with studies performed at baseline and week 24. Image analysis was performed in a blinded fashion by a core laboratory.

RESULTS Of the 282 randomized patients, 57 (20%) participated in the substudy, and of those, 50 (88%) completed both baseline and week 24 CMR. Baseline characteristics of the CMR cohort were similar to the overall study population. Of these 50 patients, 21 received aficamten and 29 received placebo. Relative to placebo, patients receiving aficamten demonstrated significant reductions (Δ least-squares mean) in LV mass index (−15 g/m^2; 95% CI: −25 to −6 g/m^2; $P = 0.001$), maximal LV wall thickness (−2.1 mm; 95% CI: −3.1 to −1.1 mm; $P < 0.001$), left atrial volume index (−13 mL/m^2; 95% CI: −19 to −7 mL/m^2; $P < 0.001$), native T1 relaxation time (−37 ms; 95% CI: −69 to −5 ms; $P = 0.026$), indexed extracellular volume fraction (−3.9 g/m^2; 95% CI: −7.0 to −0.9 g/m^2; $P = 0.014$), and indexed myocyte mass (−14 g/m^2; 95% CI: −23 to −4 g/m^2; $P = 0.004$), while there were no significant changes in LV chamber volumes, LV replacement fibrosis (late gadolinium enhancement mass −0.7 g; 95% CI: −2.9 to 1.6 g; $P = 0.54$), or extracellular volume (0.7%; 95% CI: −2.2% to 3.6%; $P = 0.61$).

CONCLUSIONS The CMR substudy of SEQUOIA-HCM demonstrated that treatment with aficamten relative to placebo for 24 weeks resulted in favorable cardiac remodeling. These changes, particularly with regard to LV mass, wall thickness, and left atrial size, could potentially lead to reduced cardiovascular events including heart failure and atrial fibrillation with longer follow-up. (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM [SEQUOIA-HCM]; NCT05186818). (JACC. 2024;■:■-■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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