Effect of Aficamten Treatment for Up to 72 Weeks on Cardiac Structure and Function in Patients with Obstructive Hypertrophic Cardiomyopathy: The SEQUOIA-HCM and FOREST-HCM CMR Sub-studies

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BACKGROUND AND METHODS

Aficamten is a next-in-class cardiac myosin inhibitor in development for the treatment of HCM

SEQUOIA-HCM (NCT05186818)

was a phase 3 trial of aficamten vs placebo in patients with obstructive HCM (oHCM), with an optional CMR sub-study over 24 weeks[1]

FOREST-HCM (NCT04848506)

is an open-label extension study of aficamten in patients with HCM, with an optional CMR sub-study

Between May 2021 and February 2025, 350 patients with oHCM were enrolled in FOREST-HCM

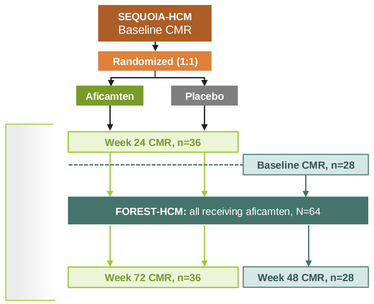
By February 18th, 102 patients consented to participate in the CMR sub-study

64 patients completed a baseline CMR and week 48-72 CMR:

36 | from SEQUOIA-HCM with baseline CMR at the start of that study (follow-up 72 weeks)

28 | had baseline CMR at start of FOREST-HCM (follow-up 48 weeks)

Figure 1. Study Schema



HCM: hypertrophic cardiomyopathy; CMR: cardiac magnetic resonance imaging

Table 1. FOREST-HCM Baseline Characteristics

Characteristic	Non-CMR oHCM cohort (N=286)	CMR oHCM cohort (N=64)
Age, years, mean (SD)	60.9 (12.9)	59.6 (11.3)
Female, n (%)	128 (44.8)	30 (46.9)
Race, %, White/Black/Asian/Other	94/2/2/2	95/0/5/0
BMI, kg/m², mean (SD)	28.8 (4.19)	29.0 (3.58)
NYHA class, n (%)		
Class I	10 (3.5)	2 (3.1)
Class II	173 (60.5)	33 (51.6)
Class III	103 (36.0)	29 (45.3)
Family history of HCM, n (%)	77 (26.9)	15 (23.4)
Time from HCM diagnosis, years, mean (SD)	6.7 (6.34)	6.2 (5.3)
Beta-blocker, n (%)	163 (57.0)	44 (68.8)
Calcium channel blocker, n (%)	50 (17.5)	14 (21.9)
Disopyramide, n (%)	36 (12.6)	8 (12.5)

BMI, body mass index; NYHA, New York Heart Association; SD, standard deviation

RESULTS

Table 2. Hemodynamic, Biomarker, and Clinical Changes in the Overall Population and CMR Subgroup

	Non-CMR oHCM cohort N=286				CMR oHCM cohort N=64			
Characteristic	**Baseline**	**Week 48**	**Δ**	***P* value**	**Baseline**	**Week 48**	**Δ**	***P* value**
LVEF, %[a]	68.5 (5.8)	64.2 (5.6)	-4.3 (6.1)	<0.0001	67.6 (5.5)	64.3 (5.6)	-3.3 (6.4)	<0.0001
Resting LVOT-G, mmHg[a]	53.3 (35.0)	14.4 (13.2)	-39.5 (35.7)	<0.0001	66.5 (42.3)	16.4 (17.1)	-50.2 (38.9)	<0.0001
Valsalva LVOT-G, mmHg[a]	94.1 (41.9)	29.8 (25.6)	-63.9 (43.1)	<0.0001	94.4 (44.9)	33.8 (30.7)	-60.6 (48.0)	<0.0001
NT-proBNP, pg/mL[b]	757 (361, 1544)	131 (67, 343)	-609 (-1328, -232)	<0.0001	740 (289, 1414)	99 (52.5, 213)	-492 (-1093, -230)	0.0005
hs-TnI, ng/L[b]	10.7 (5.8, 19.1)	5.4 (3.5, 10.1)	-3.9 (-10.30, -1.0)	<0.0001	13.6 (5.5, 30.2)	6.4 (3.6, 11.2)	-7.3 (-17.8, -1.3)	0.0027
KCCQ-CSS[a]	70.0 (19.4)	86.2 (15.2)	15.5 (17.5)	<0.0001	72.3 (19.3)	86.7 (15.1)	14.3 (15.6)	<0.0001
≥1 NYHA FC improvement, % (95% CI)			76.9 (71.0, 82.8)	<0.0001			73.4 (62.3, 84.6)	<0.0001

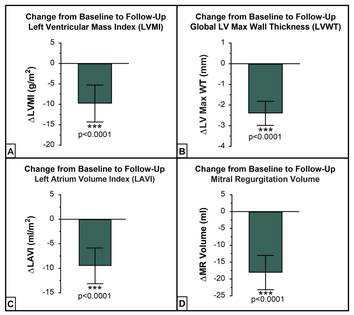
[a]Mean (SD) [b]Median (IQR)
hsTnI, high-sensitivity troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; NYHA FC, New York Heart Association functional class; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Table 3. Aficamten Effects on Cardiac Structure and Function as Measured by CMR at Week 48

Variable[a]	Baseline	Change from baseline	*P* value
LVMI, g/m²	104.4 (28.8)	-9.8 (18.1)	<0.0001
Maximal WT, mm	18.8 (3.8)	-2.4 (2.3)	<0.0001
LAVI, mL/m²	62.6 (20.3)	-9.5 (14.1)	<0.0001
LAV, mL	123.7 (42.9)	-17.9 (28.3)	<0.0001
MR volume, mL	28.4 (18.7)	-18.1 (19.2)	<0.0001
MR fraction, %	26.7 (15.1)	-14.2 (15.6)	<0.0001

[a]Mean (SD)
LAV, left atrial volume; LAVI, left atrial volume index; LVMI, left ventricular mass index; MR, mitral regurgitation; WT, wall thickness.

Figure 2. Aficamten Normalizes Measures of Cardiac Structure and Function as Measured by CMR From Baseline to Follow-up



Depicted: Mean ±95% CI

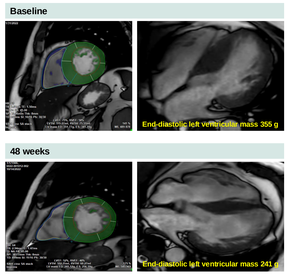
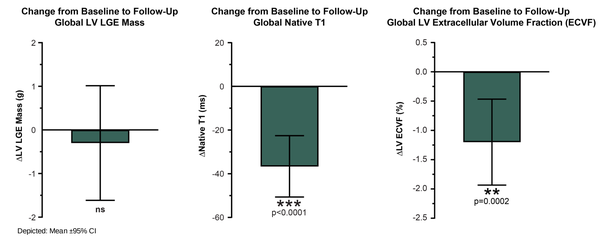


Table 4. Aficamten Effects on Myocardial Fibrosis as Assessed by CMR

Variable[a]	N	Baseline	Change from baseline	*P* value
Absolute LGE Mass, g	61	4.1 (4.4)	-0.3 (5.0)	0.52
LGE proportion of LV mass, %	60	2.9 (3.3)	-0.2 (3.9)	0.54
Native T1, ms	63	1047.8 (95.5)	-36.6 (55.7)	<0.0001
Global ECV, %	60	28.1 (3.6)	-1.2 (2.8)	0.0002

[a]Mean (SD)
ECV, extracellular volume; LGE, late gadolinium enhancement; LV, left ventricle

Figure 3. Absence of Replacement Fibrosis Progression and Reduction of Interstitial Fibrosis as Measured by CMR while on Aficamten from Baseline to Follow-up



Depicted: Mean ±95% CI

Figure 4. Reduction in MR Severity with Aficamten as Measured by CMR at Week 48

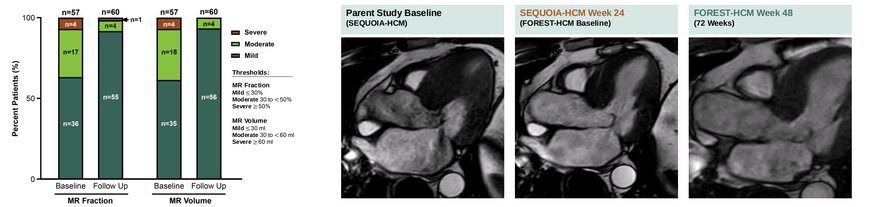
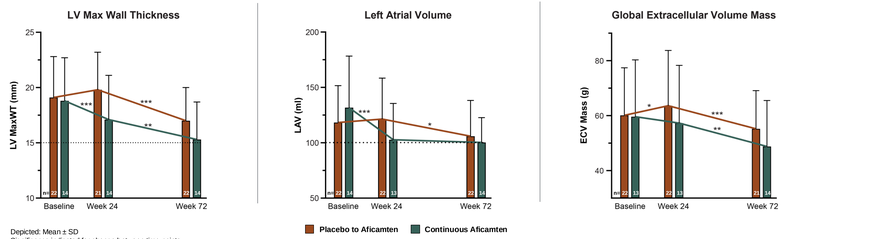


Figure 5. Evaluation for Progressive Cardiac Structural Changes on CMR: Placebo to Aficamten Cross-Over (Delayed Start) vs. Continuous Aficamten (Early Start) at Week 48 and 72



Depicted: Mean ± SD
Significance indicated for change between time points
*p<0.05 **p<0.001 *** p<0.0001
LV, left ventricle; MaxWT, maximum wall thickness; LAV, left atrial volume; ECV, extracellular volume

CONCLUSIONS

Longer-term treatment with aficamten over 48-72 weeks resulted in

- Favorable cardiac structural remodeling with reduction in LV mass and LA size
- Reduction in mitral regurgitation
- No progression of replacement myocardial fibrosis (LGE)
- <u>Progressive</u> reduction in interstitial myocardial fibrosis (ECV)

These favorable structural changes were complemented by an improvement in:

- symptoms
- patient-reported outcomes
- hemodynamics, and
- biomarkers (similar to those benefits seen in the non-CMR study participants)

The 5-year CMR sub-study of FOREST-HCM is ongoing and will continue to evaluate the effects of aficamten as a potential disease-modifying agent in HCM

Reference

[1]Masri et al. *JACC* 2024;84:1086-17.

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