Global Remodeling Changes with Aficamten in Patients with Obstructive Hypertrophic Cardiomyopathy: An Analysis of the SEQUOIA-HCM Trial

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Background

- Obstructive hypertrophic cardiomyopathy (oHCM) is characterized by hyperdynamic left ventricular (LV) systolic function, ventricular hypertrophy, and LV outflow tract obstruction as measured by gradient (LVOT-G).
- oHCM is heterogeneous in its expression, affecting myocardial structure and function, with adverse remodeling occurring over decades.
  - ~70–90% of oHCM patients have left ventricular hypertrophy (LVH) by ECG.[1]
  - A similar proportion of oHCM patients have abnormal NT-proBNP.[2]
- Aficamten mitigates cardiac hypercontractility and impacts adverse remodeling which may:
  - Ameliorate the progression of oHCM.
  - Portend changes in the natural history of the disease.
- Therefore, the effect of aficamten on myocardial remodeling is of primary interest to patients and providers.

ECG, electrocardiogram; NT-proBNP, N-terminal pro-B type natriuretic peptide.

1. Maron BJ, Maron MS. *Lancet* 2013; 381(9862):242-55. **2.** Rowin EJ, Maron BJ, et al. *J Am Coll Cardiol* 2018;71(12):1216-26.

Background

- Results from the phase 3 SEQUOIA-HCM trial (NCT05186818) met the primary endpoint demonstrating that in patients with symptomatic oHCM, aficamten[1]:
  - Improved exercise capacity (primary endpoint)
  - Reduced symptoms
  - Reduced LVOT-G

Change from baseline to Week 24 in pVO_2 using CPET

1.8 mL/kg/min for aficamten
vs
0.0 mL/kg/min for placebo

LS mean difference (SE) 1.7 (0.36) mL/kg/min

P<0.001

Change from baseline to Week 24 in KCCQ-CSS

11 points for aficamten
vs
5 points for placebo

LS mean difference was 7 points

P<0.001

Change from baseline to Week 24 in Valsalva LVOT-G

–47.6 mmHg for aficamten
vs
–1.8 mmHg for placebo

LS mean difference was –50 mmHg

P<0.001

CPET, cardiopulmonary exercise testing; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LS, least squares; pVO_2, peak oxygen consumption.

1. Maron MS, et al. N Engl J Med 2024;390:1849-61.

Objectives

- To characterize the impact of aficamten treatment compared with placebo in patients with oHCM with respect to structural and functional changes over 24 weeks.
- This study specifically focused on clinical data from a remodeling perspective, including changes from baseline throughout the SEQUOIA-HCM trial in:
  - LV wall thickness
  - Left atrial volume index (LAVi)
  - Hyperdynamic LV systolic function
  - Abnormal ECG
  - Cardiac biomarkers (NT-proBNP)

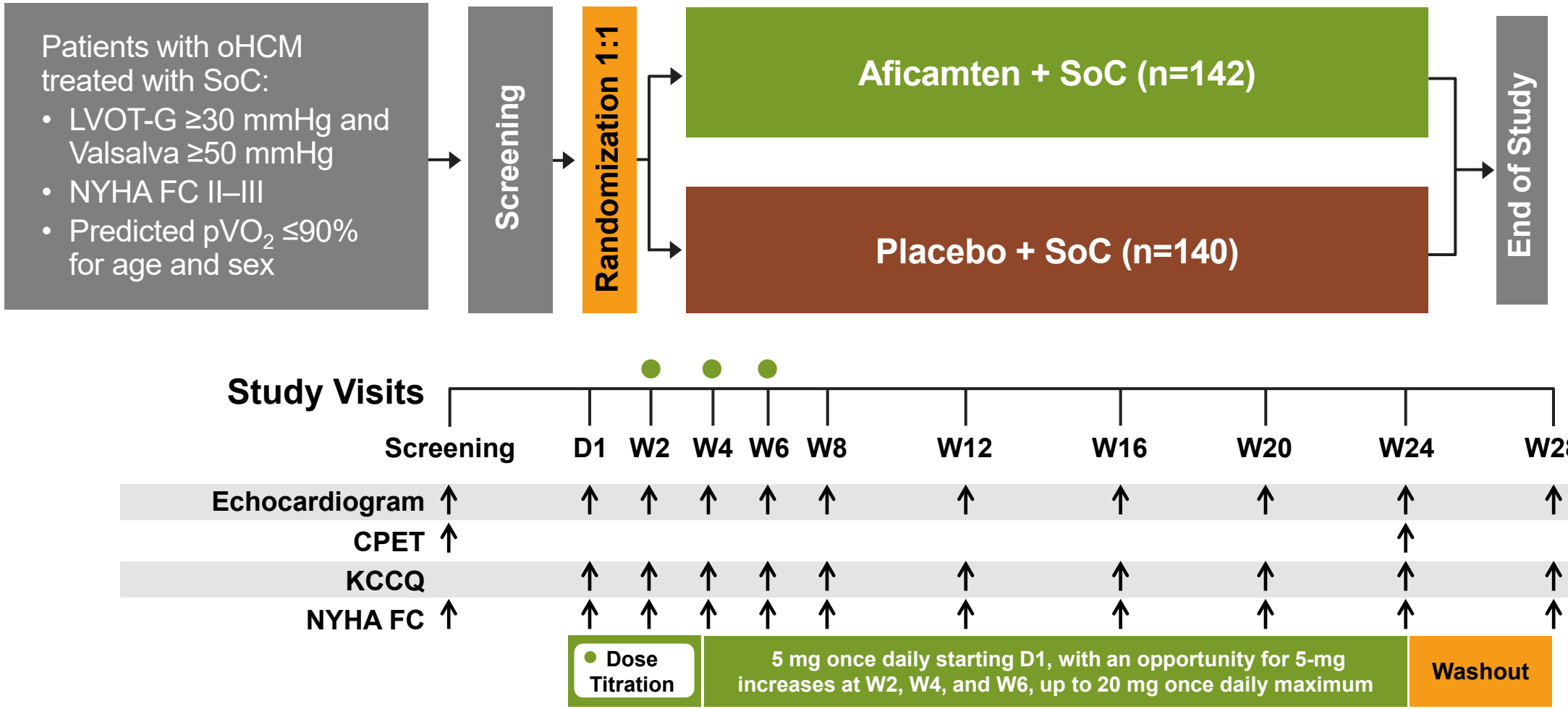
LV, left ventricular.

Methods: Study Design

- SEQUOIA-HCM recruited 282 patients with symptomatic oHCM.
- Patients were characterized by:
  - New York Heart Association (NYHA) functional class II–III.
  - LVOT-G ≥30 mmHg at rest and ≥50 mmHg with Valsalva.
  - Baseline pVO_2 ≤90% for age and sex.
  - Respiratory exchange ratio (RER) ≥1.05.
- Patients received aficamten (5–20 mg), titrated based on site-read echocardiogram findings to individually achieve LVOT-G ≤30 mmHg while maintaining LVEF ≥50% compared with placebo.

LVEF, left ventricular ejection fraction.

Methods: SEQUOIA-HCM Study Design[1,2]



D, day; NYHA FC, New York Heart Association functional class; SoC, standard of care; W, week.

1. Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215. **2.** Maron MS, et al. *N Engl J Med* 2024;390(20):1849-61.

Methods

- Global remodeling response after 24 weeks of treatment of aficamten vs placebo was assessed across 5 domains, reflecting structural, electrophysiologic, and biochemical disease expression.

1. Change in maximal wall thickness (MWT) ≥1.5 mm.
2. Change in the categorical degree of left atrial enlargement according to LAVi[1]:
   - Normal, 16–34 mL/m^2
   - Mild, 35–41 mL/m^2
   - Moderate, 42–48 mL/m^2, or
   - Severe enlargement, >48 mL/m^2
3. Presence or absence of hyperdynamic LVEF ≥72%, assessed by the core laboratory.
4. Presence or absence of LVH on ECG per the core laboratory.
5. Reduction of NT-proBNP by ≥50% from baseline, or any increase.

1. Lang RM, et al. *J Am Soc Echocardiogr* 2015;28(1):1-39.e14.

Results: Baseline Characteristics

- There were no baseline differences between aficamten and placebo in any of the 5 domains.

	Placebo, n=140	Aficamten, n=142
Age, y	59.0 ± 13.4	59.2 ± 12.6
Female sex, n (%)	59 (42.1)	56 (39.4)
Race, n (%)		
White	115 (82.1)	108 (76.1)
Geographic region, n (%)		
North America	45 (32.1)	49 (34.5)
China	22 (15.7)	24 (16.9)
Europe and Israel	73 (52.1)	69 (48.6)
Medical history, n (%)		
Hypertension	70 (50.0)	75 (52.8)
Paroxysmal atrial fibrillation	20 (14.3)	21 (14.8)
Permanent atrial fibrillation	1 (0.7)	2 (1.4)
CPET		
pVO_2 (mL/kg/min)	18.6 (4.5)	18.5 (4.5)
Percent of predicted pVO_2 (%)	57 (12)	58 (13)

Values are the mean ± SD unless otherwise indicated.

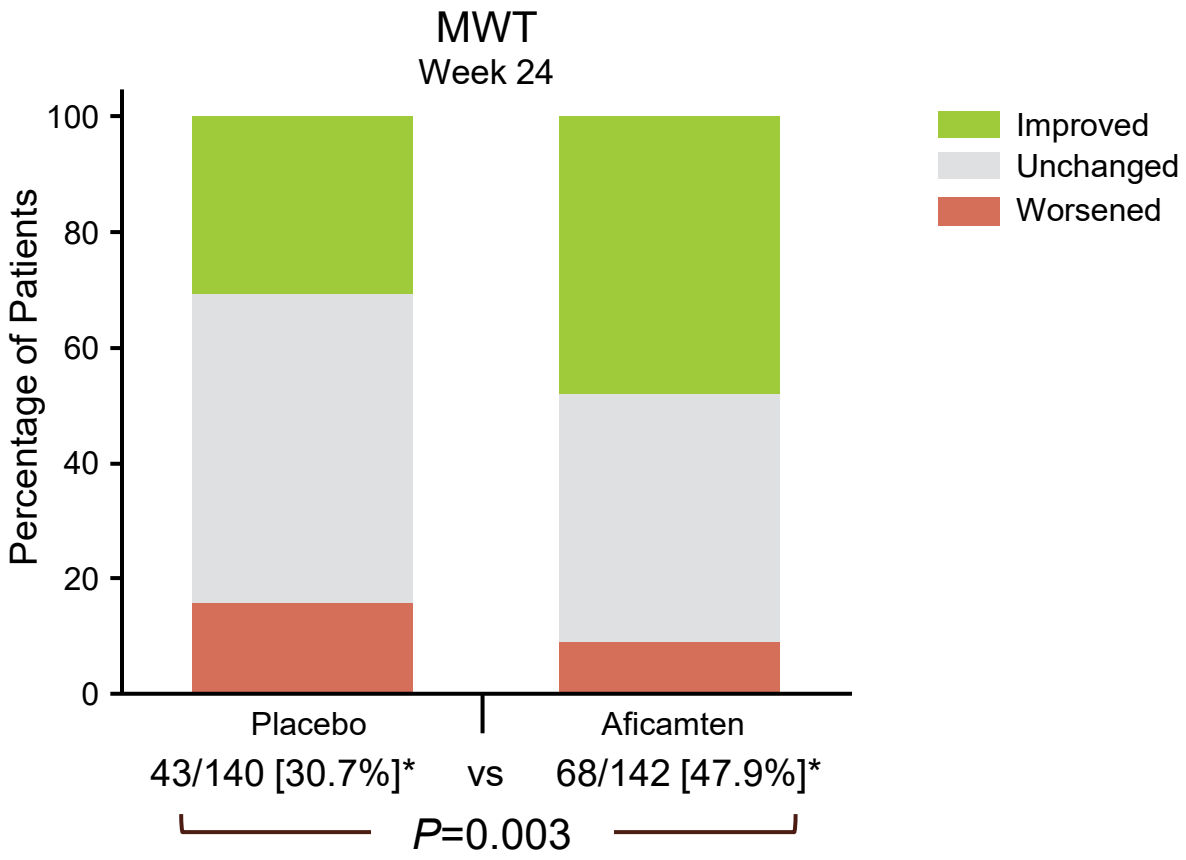
	Placebo, n=140	Aficamten, n=142
Background HCM therapy, n (%)		
Beta-blocker	87 (62.1)	86 (60.6)
Calcium channel blocker	36 (25.7)	45 (31.7)
Disopyramide	20 (14.3)	16 (11.3)
None	22 (15.7)	19 (13.4)
KCCQ-CSS	74 ± 18	76 ± 18
NYHA FC, n (%)		
II	106 (75.7)	108 (76.1)
III/IV	34 (24.3)	34 (23.9)
Median NT-proBNP (IQR), pg/mL	692 (335–1795)	818 (377–1630)
Median hs-cTnI (IQR), ng/L	11.5 (7.7–25.0)	12.9 (7.6–33.6)
Echocardiographic parameters		
Valsalva LVOT-G, mmHg	83.3 ± 33	82.9 ± 32
Resting LVOT-G, mmHg	55.3 ± 32	54.8 ± 27
LVEF, %	74.8 ± 6.3	74.8 ± 5.5
LVEF ≥ 72%	101 (72.1)	102 (71.8)
Maximal LV wall thickness, mm	21.0 ± 3.0	20.7 ± 3.0
LVMI, g/m²	134.6 ± 36.6	129.6 ± 31.0
LAVi, mL/m²	40.9 ± 15.1	40.1 ± 12.7
LVH by ECG	63 (50.4)	70 (53.4)

hs-cTnI, high-sensitivity cardiac troponin I; IQR, interquartile range; LVMI, ventricular mass index.

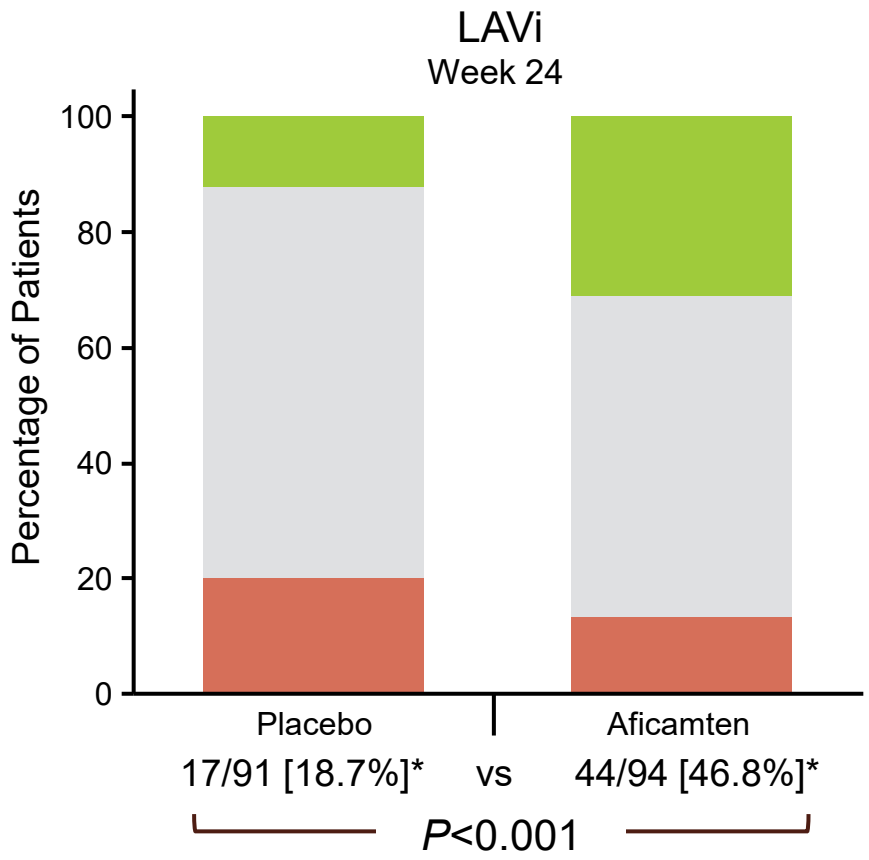
Global Remodeling Clinical Domains at Week 24: MWT and LAVi

- Significant improvements in individual remodeling domains observed for aficamten vs placebo:

Any improvement in MWT



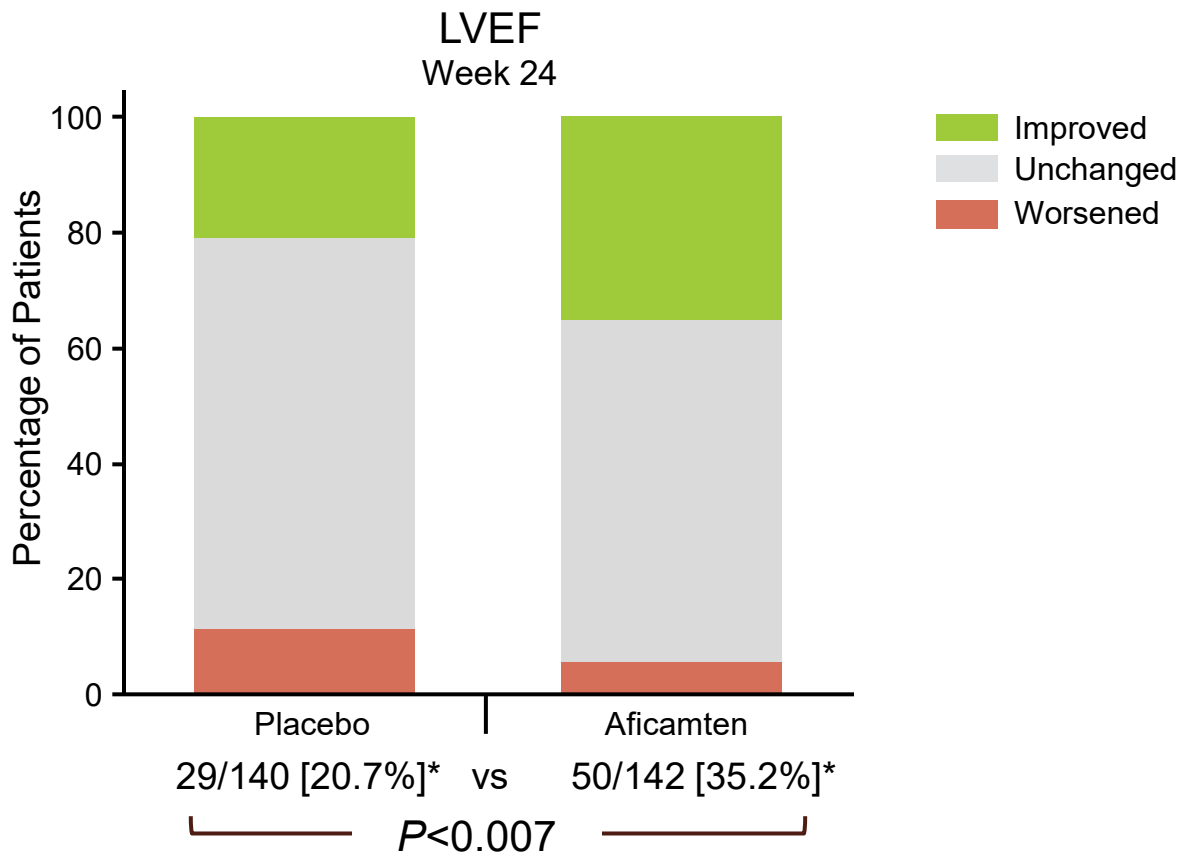
Improvement by ≥1 category in LAVi among patients with abnormal LAVi (>34 mL/m^2) at baseline



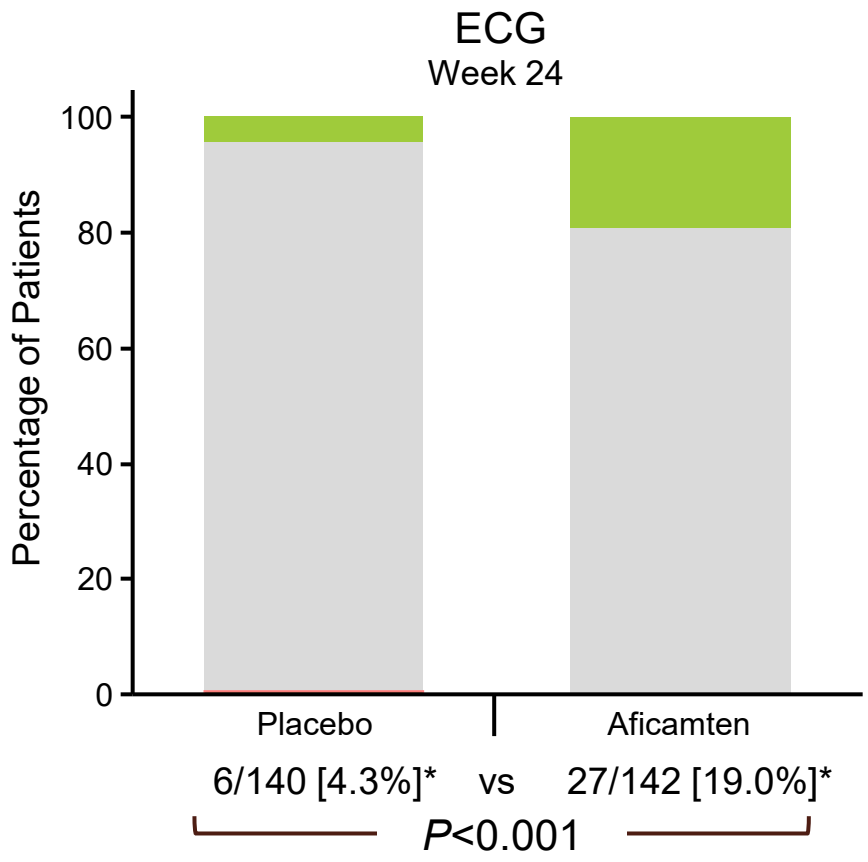
*Patients with improvement. The full analysis set of 282 patients (140 placebo; 142 aficamten) are displayed for each domain. For each metric, the remodeling response was assigned a +1 if improvement was noted, 0 if no change was seen, and –1 if the metric worsened.

Global Remodeling Clinical Domains at Week 24: LVEF and ECG

Normalization of systolic function (LVEF 50% to <72%)

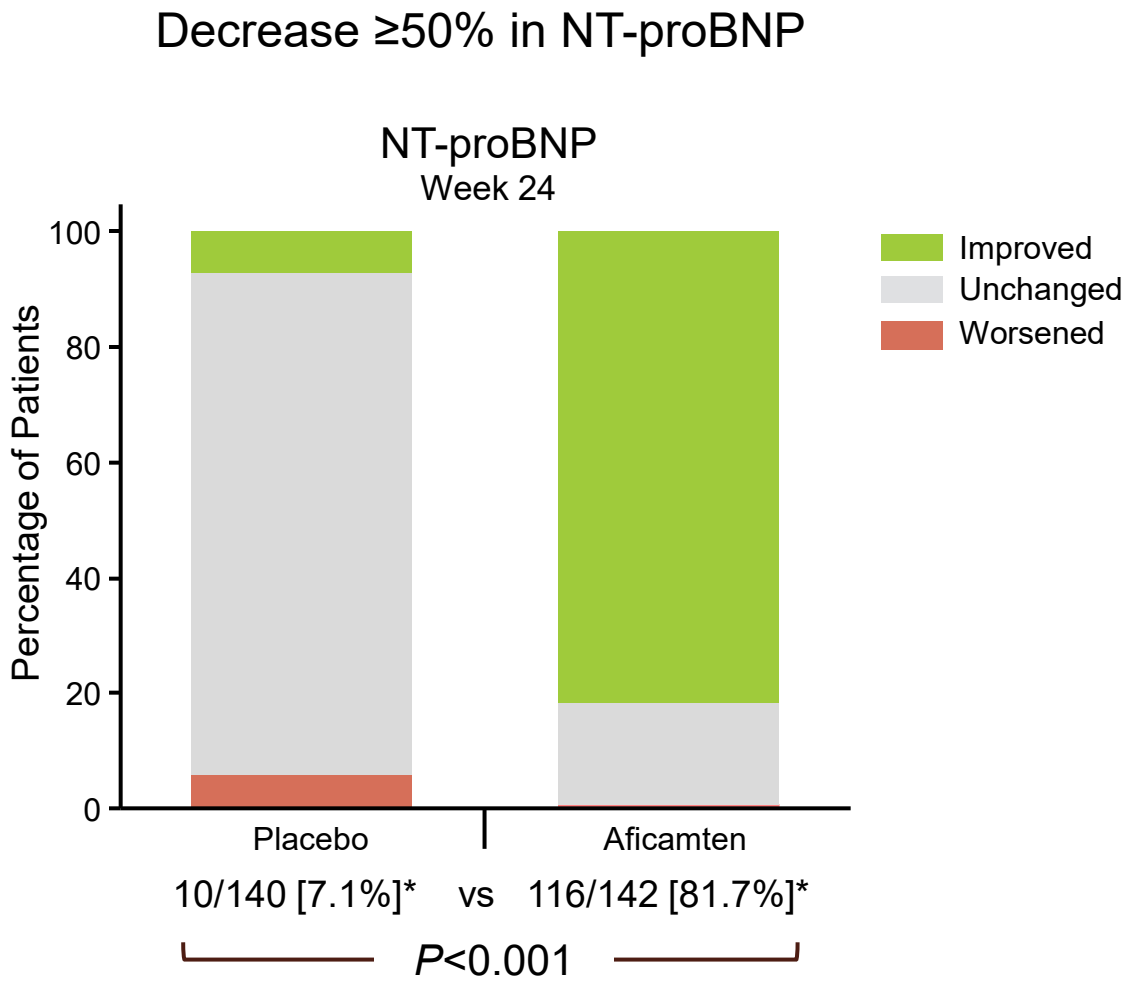


Resolution of strain pattern on ECG by core laboratory assessment



*Patients with improvement. The full analysis set of 282 patients (140 placebo; 142 aficamten) are displayed for each domain.
For each metric, the remodeling response was assigned a +1 if improvement was noted, 0 if no change was seen, and –1 if the metric worsened.

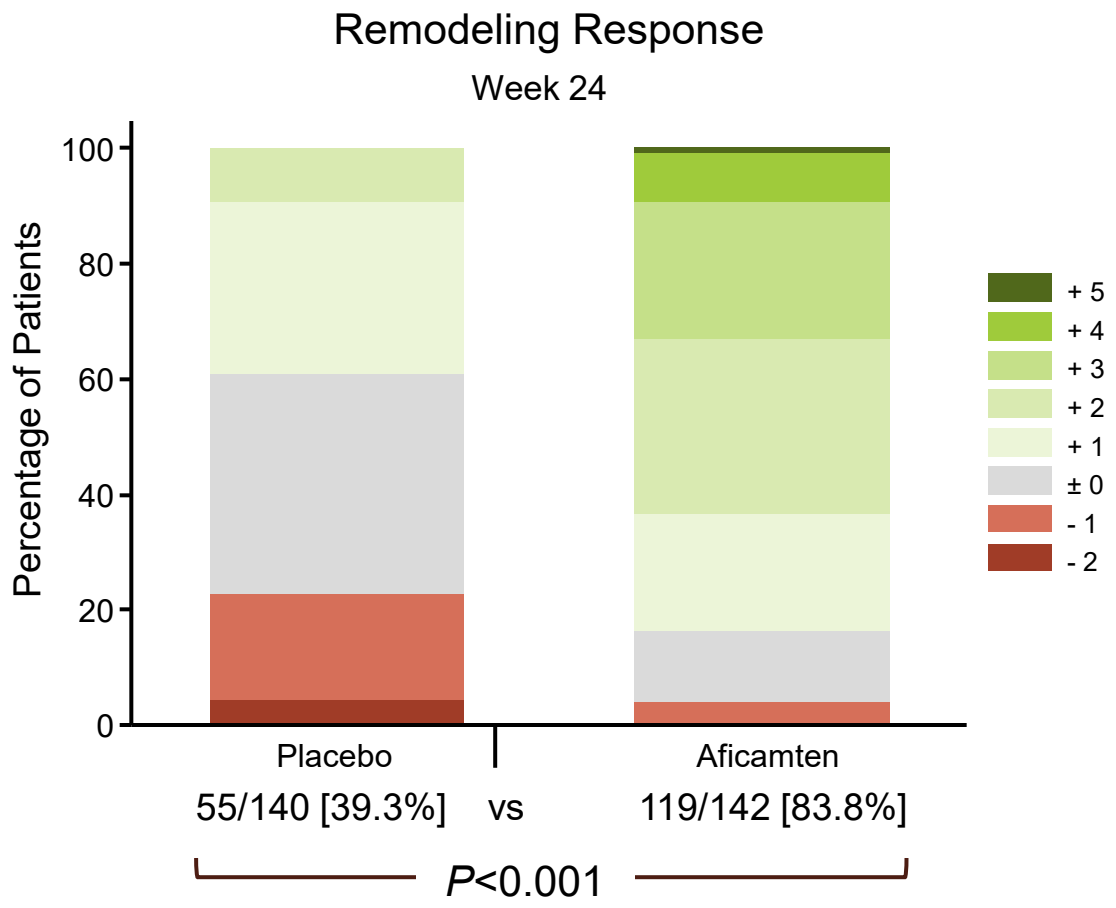
Global Remodeling Clinical Domains at Week 24: NT-proBNP



*Patients with improvement. The full analysis set of 282 patients (140 placebo; 142 aficamten) are displayed for each domain.
For each metric, the remodeling response was assigned a +1 if improvement was noted, 0 if no change was seen, and –1 if the metric worsened.

Global Remodeling Clinical Domains at Week 24: Remodeling Response

- Overall, patients treated with aficamten had beneficial remodeling in ≥1 of 5 domains vs placebo.



These data yielded a number needed to treat of 2.2 persons to improve on at least 1 remodeling variable.

The full analysis set of 282 patients (140 placebo; 142 aficamten) are displayed for each domain.
For each metric, the remodeling response was assigned a +1 if improvement was noted, 0 if no change was seen, and –1 if the metric worsened.

Conclusions

- Treatment with aficamten resulted in beneficial changes in indices of global remodeling as assessed using multiple domains encompassing:
  - Cardiac structure and function
  - Electrophysiology
  - Biochemistry
- These findings suggest that remodeling response begins early after treatment and is experienced by the majority of aficamten treated patients with symptomatic oHCM at baseline.
- Long-term studies such as FOREST-HCM may help elucidate how these findings impact clinical outcomes.

Disclosures and Acknowledgments

Disclosures

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