Impact of Aficamten on Echocardiographic Cardiac Structure and Function in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

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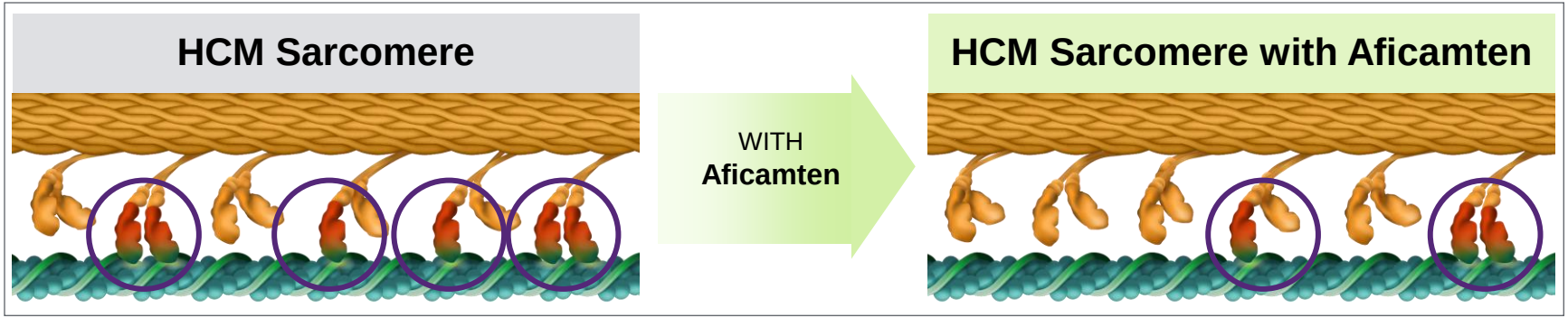
Background

- Aficamten is a next-in-class cardiac myosin inhibitor, a small-molecule selective inhibitor of the cardiac myosin ATPase, which reduces contractility by reversibly binding to cardiac myosin and reducing excessive myosin-actin cross-bridges.



- In the phase 3, multicenter, randomized, double-blinded, placebo-controlled SEQUOIA-HCM study, aficamten improved exercise capacity (pVO2) and lowered resting and Valsalva LVOT gradients in adults with symptomatic obstructive HCM (oHCM).

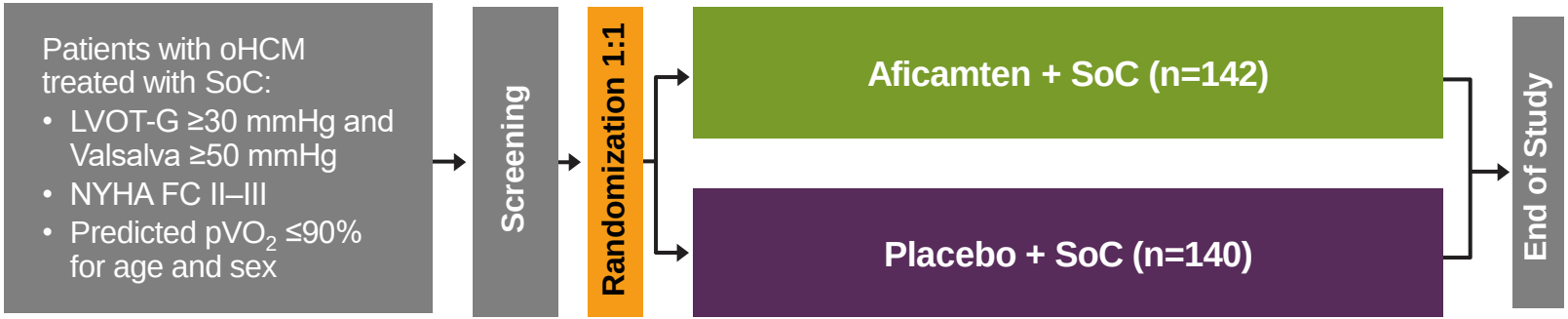
Maron MS, et al. *N Engl J Med* 2024;390(20):1849-61.
HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract.

Purpose

- To evaluate the effect of aficamten on echocardiographic measures of cardiac structure and function in SEQUOIA-HCM.

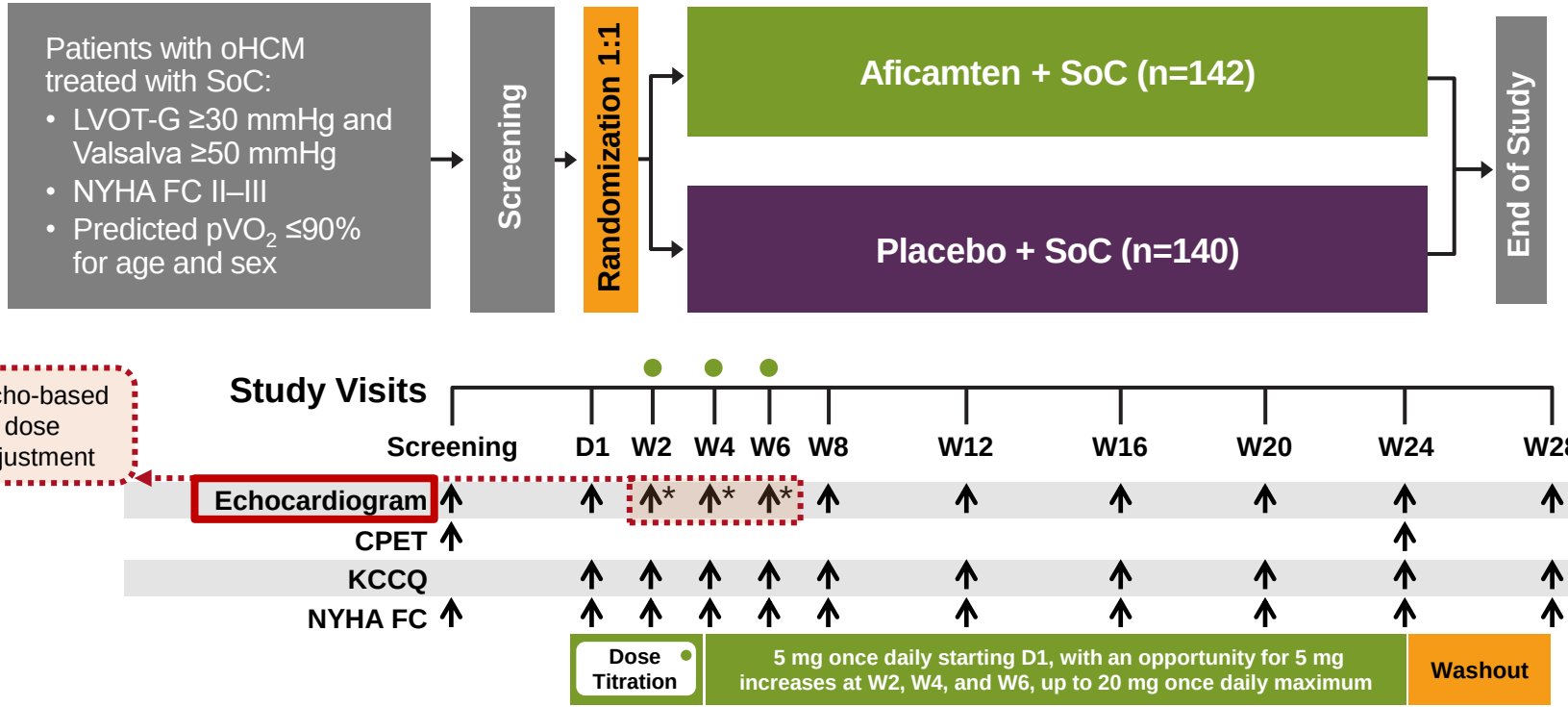
- To assess the relationship between changes in echocardiographic measures with changes in pVO_2 and other outcomes.

Methods: SEQUOIA-HCM Study Design



CPET, cardiopulmonary exercise testing; D, day; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT-G, left outflow tract gradient; NYHA FC, New York Heart Association functional class; SoC, standard of care; W, week. Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215.

Methods: SEQUOIA-HCM Study Design



Echocardiographic measurements were performed by a core imaging laboratory.

CPET, cardiopulmonary exercise testing; D, day; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT-G, left outflow tract gradient; NYHA FC, New York Heart Association functional class; SoC, standard of care; W, week. Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215.

Results: Baseline Characteristics

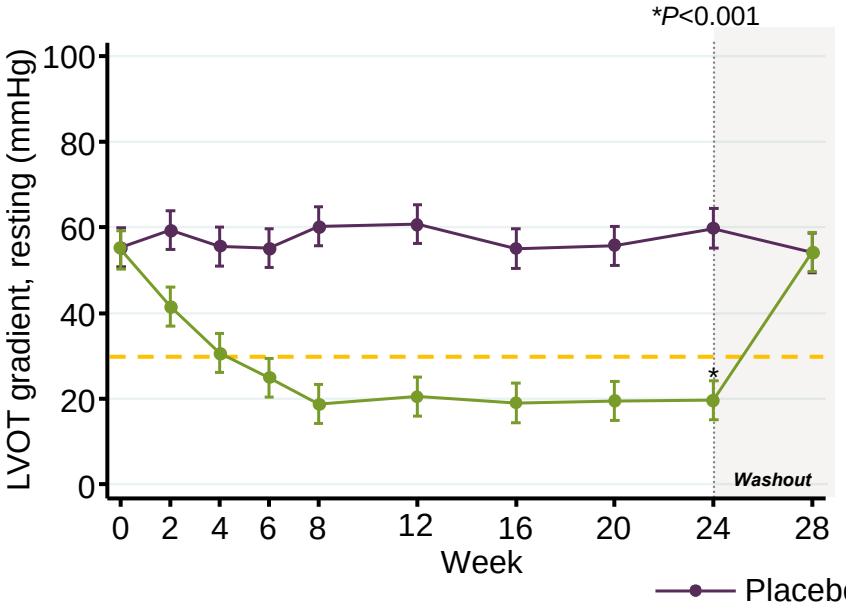
Characteristic	Aficamten n=142	Placebo n=140
Age, mean ± SD, y	59 ± 13	59 ± 13
Female sex, n (%)	56 (39)	59 (42)
Race, n (%)		
White	108 (76)	115 (82)
Asian	29 (20)	25 (18)
Black	3 (2)	0
Other	2 (1)	0
Geographic region, n (%)		
North America	49 (35)	45 (32)
China	24 (17)	22 (16)
Rest of World	69 (49)	73 (52)
Medical history, n (%)		
Hypertension	75 (53)	70 (50)
Family history of HCM	41 (29)	34 (24)
Coronary artery disease	19 (13)	16 (11)
Paroxysmal atrial fibrillation	21 (15)	20 (14)
Diabetes	14 (10)	16 (11)
Permanent atrial fibrillation	2 (1)	9 (6)

Characteristic	Aficamten n=142	Placebo n=140
Background HCM therapy, n (%)		
Beta-blocker	86 (61)	87 (62)
Calcium channel blocker	45 (32)	36 (26)
Disopyramide	16 (11)	20 (14)
None	19 (13)	22 (16)
KCCQ-CSS, mean ± SD	76 ± 18	74 ± 18
NYHA FC at baseline, n (%)		
Class II	108 (76)	106 (76)
Class III	34 (24)	33 (24)
Class IV	0	1 (1)
NT-proBNP, median [IQR], pg/mL	818 [377–1630]	692 [335–1795]
BMI (kg/m^2), mean ± SD	28.0 ± 3.8	28.2 ± 3.7
Resting heart rate, mean ± SD, beats per minute	69 ± 11	71 ± 13
Systolic blood pressure, mean ± SD, mmHg	125 ± 16	126 ± 16
Diastolic blood pressure, mean ± SD, mmHg	75 ± 11	74 ± 11

BMI, body mass index; CSS, clinical summary score; NT-ProBNP, N-terminal pro-B-type natriuretic peptide.

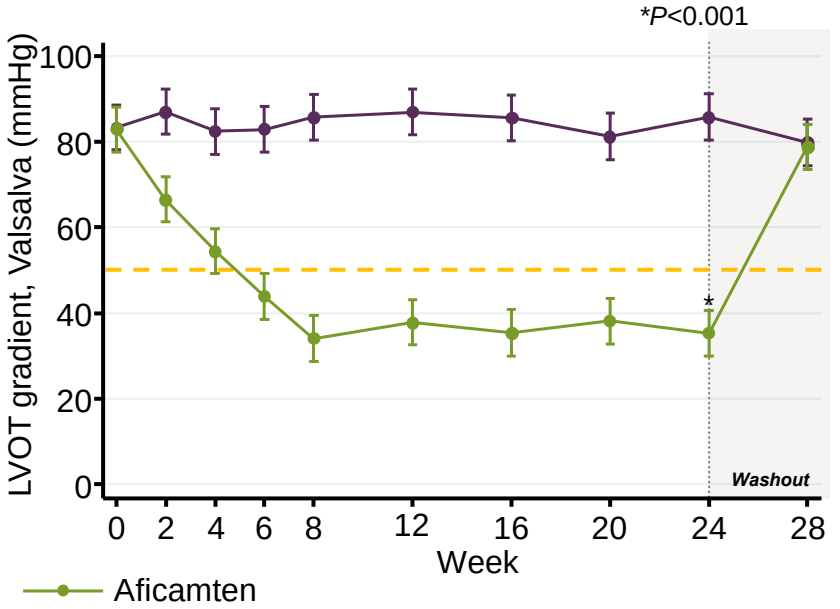
Results: Effect of Aficamten on LVOT Gradients

LVOT Gradient (Rest)



−40 mmHg (−46, −34) (24 weeks)

LVOT Gradient (Valsalva)

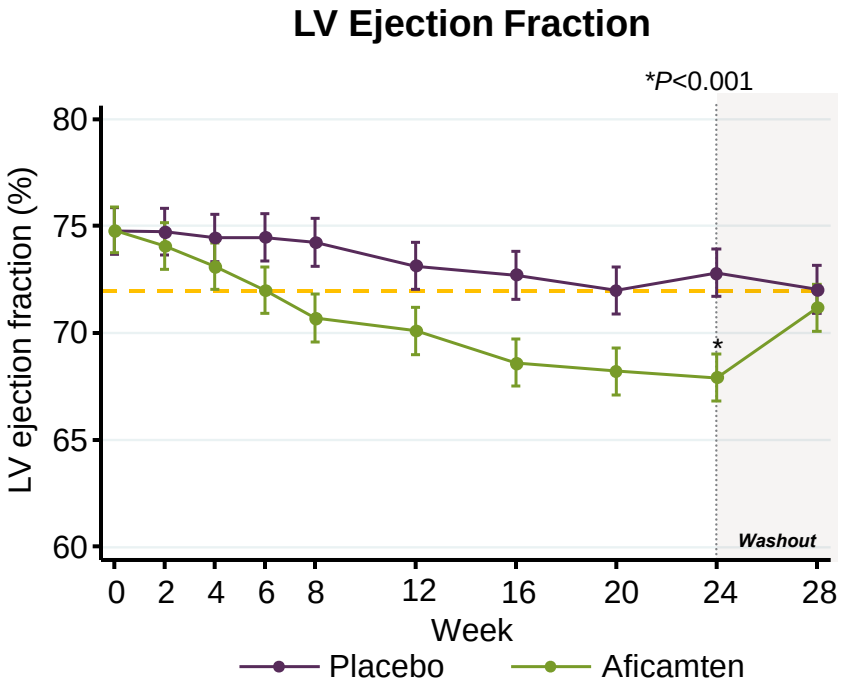


−50 mmHg (−57, −44) (24 weeks)

Maron MS, et al. *N Engl J Med* 2024;390(20):1849-61.

P values reflect placebo-corrected treatment difference at Week 24 compared with baseline adjusted for stratification by beta-blockers and CPET mode (bicycle vs treadmill).

Results: Effect of Aficamten on LV Systolic Function



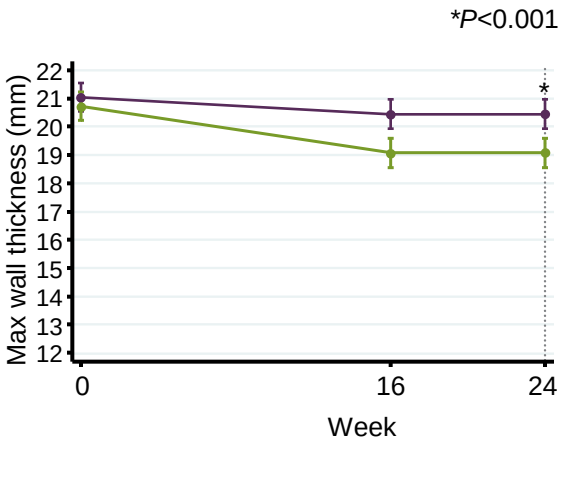
−4.8% (−6.4, −3.3) (24 weeks)

Maron MS, et al. *N Engl J Med* 2024;390(20):1849-61.

P values reflect placebo-corrected treatment difference at Week 24 compared with baseline adjusted for stratification by beta-blockers and CPET mode (bicycle vs treadmill). LV, left ventricle.

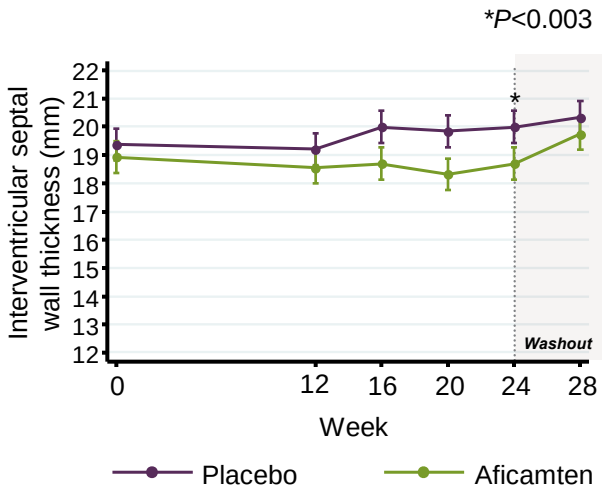
Results: Effect of Aficamten on LV Structure

Max Wall Thickness[a]



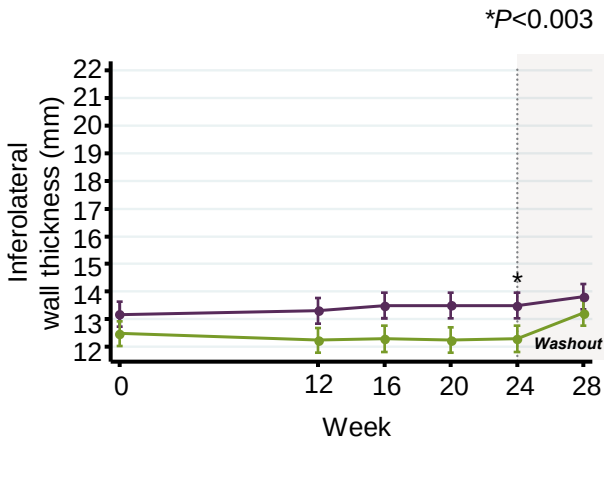
− 1.2 mm (−1.8, −0.6) (24 weeks)

Septal Wall Thickness



−1.0 mm (−1.6, −0.3) (24 weeks)

Inferolateral Wall Thickness



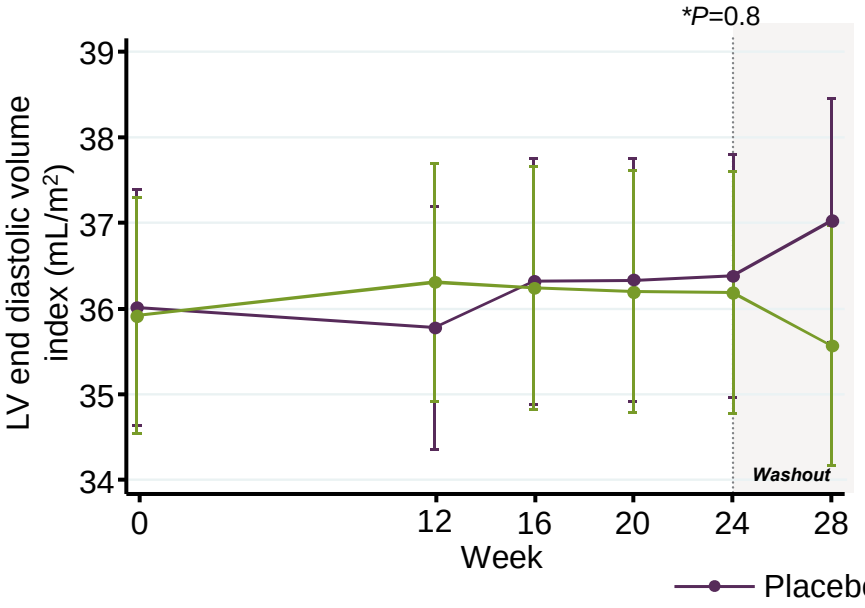
−0.8 mm (−1.3, −0.3) (24 weeks)

[a] Only measured at Weeks 0, 16, 24.

P values reflect placebo-corrected treatment difference at Week 24 compared with baseline adjusted for stratification by beta-blockers and CPET mode (bicycle vs treadmill).

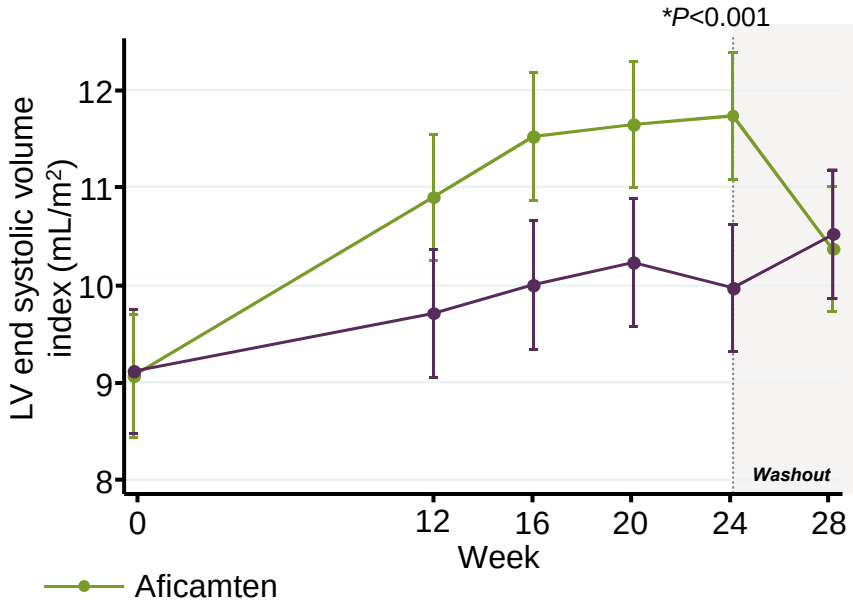
Results: Effect of Aficamten on LV Structure

LV End Diastolic Volume Index



No Change

LV End Systolic Volume Index

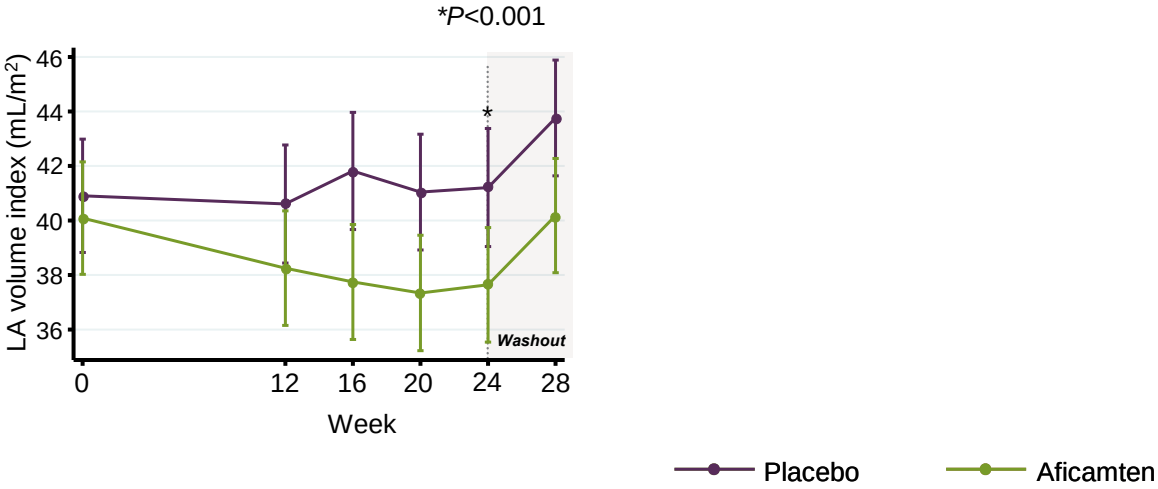


+1.7 mL/m² (1.0, 2.4) (24 weeks)

P values reflect placebo-corrected treatment difference at Week 24 compared with baseline adjusted for stratification by beta-blockers and CPET mode (bicycle vs treadmill).

Results: Effect of Aficamten on LV Diastolic Function

LA Volume Index

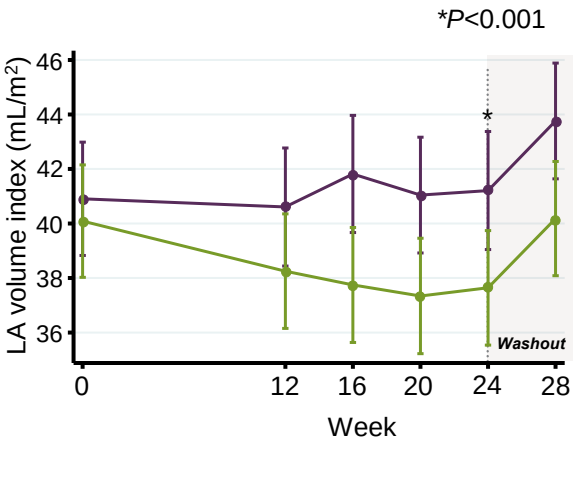


−3.8 mL/m² (−5.5, −2.2) (24 weeks)

P values reflect placebo-corrected treatment difference at Week 24 compared with baseline adjusted for stratification by beta-blockers and CPET mode (bicycle vs treadmill). e´, early diastolic mitral annular velocity; E/e´, ratio between early mitral inflow velocity and early diastolic mitral annular velocity; LA, left atrium.

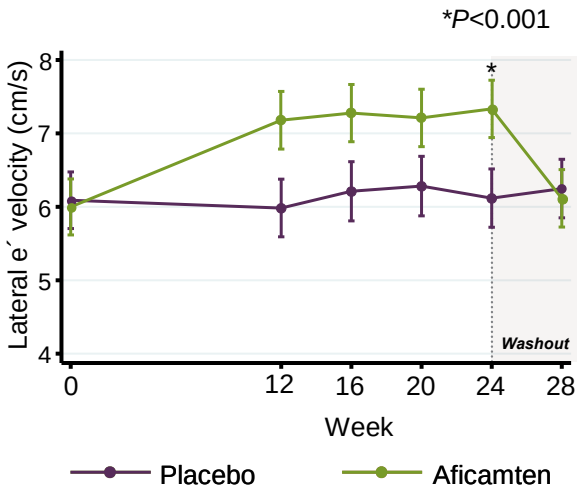
Results: Effect of Aficamten on LV Diastolic Function

LA Volume Index



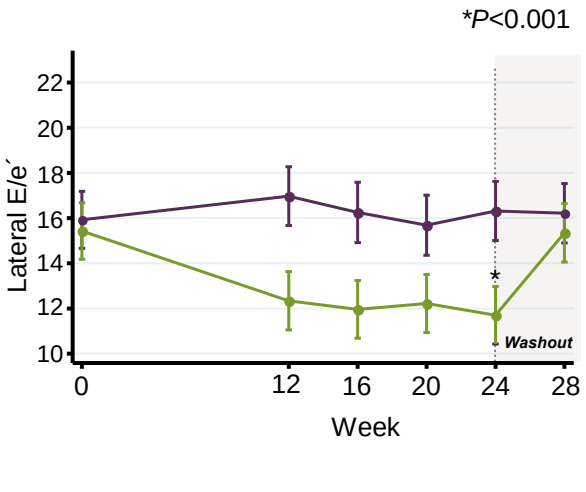
−3.8 mL/m² (−5.5, −2.2) (24 weeks)

Lateral e´ Velocity



+1.2 cm/s (0.7, 1.6) (24 weeks)

Lateral E/e´

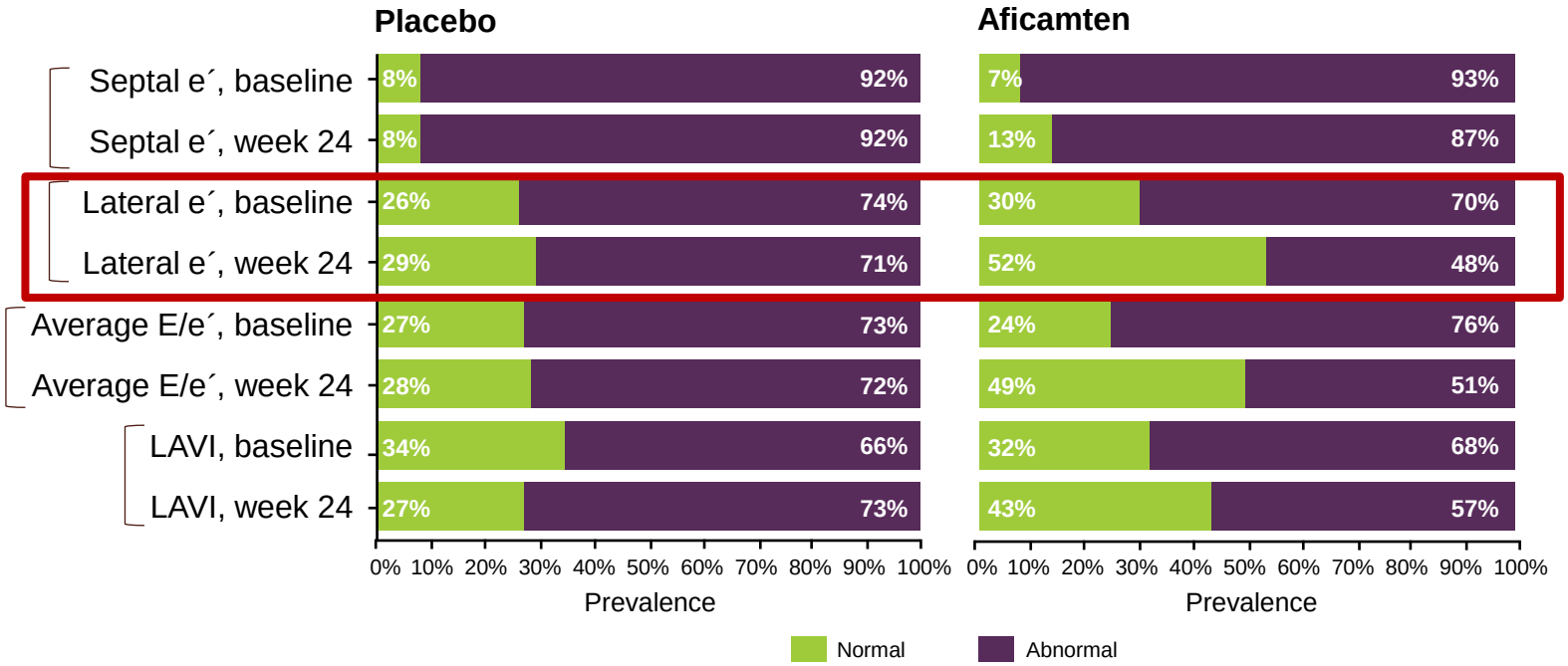


−3.9 (−5.0, −2.0) (24 weeks)

Placebo Aficamten

P values reflect placebo-corrected treatment difference at Week 24 compared with baseline adjusted for stratification by beta-blockers and CPET mode (bicycle vs treadmill). e´, early diastolic mitral annular velocity; E/e´, ratio between early mitral inflow velocity and early diastolic mitral annular velocity; LA, left atrium.

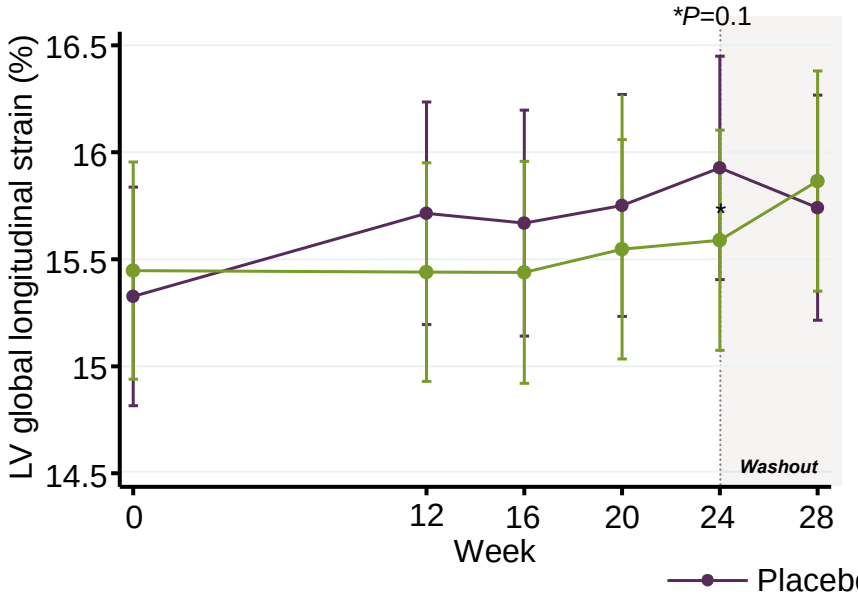
Results: Prevalence of Abnormal LV Diastolic Function Measures



LAVI, left atrial volume index.

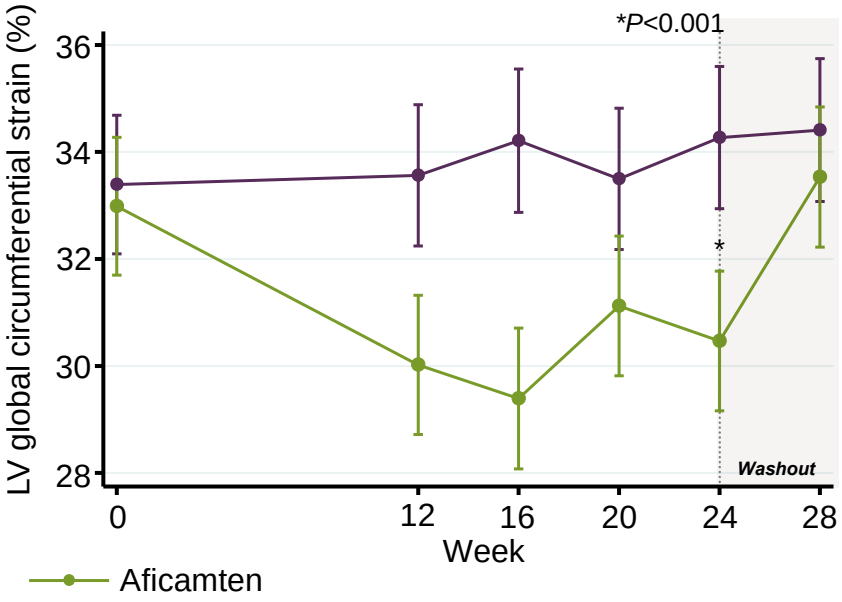
Results: Effect of Aficamten on Myocardial Deformation

LV Global Longitudinal Strain[a]



No change

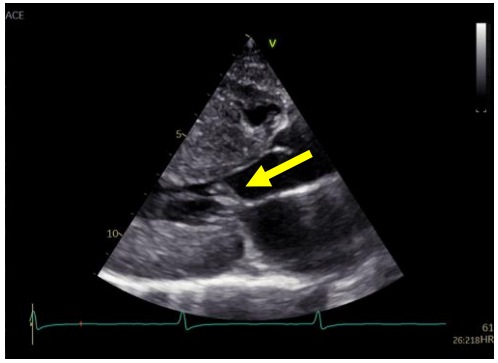
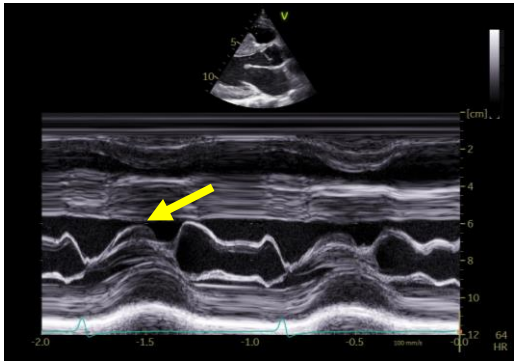
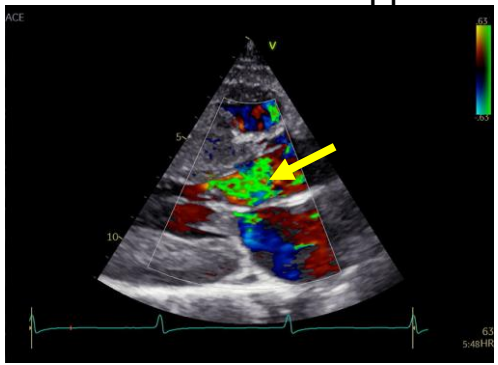
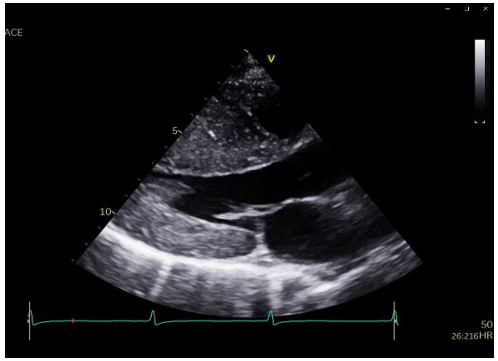
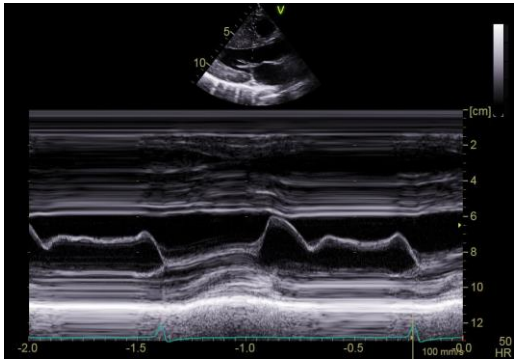
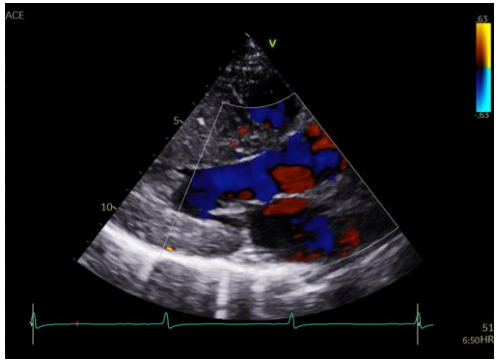
LV Global Circumferential Strain[a]



−3.7% (−5.6, −1.8) (24 weeks)

[a] Absolute strain values are presented. *P* values reflect placebo-corrected treatment difference at Week 24 compared with baseline adjusted for stratification by beta-blockers and CPET mode (bicycle vs treadmill).

Sample Aficamten Results

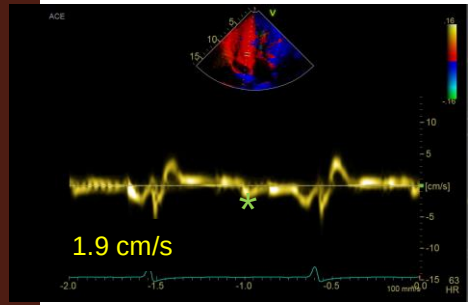
	PLAX view	PLAX M-mode	PLAX with color Doppler
Screening			
Week 24			

PLAX – Parasternal Long Axis, SAM – systolic anterior motion

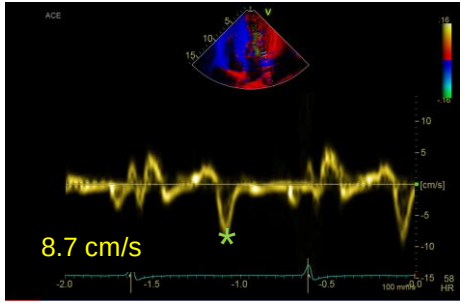
Sample Aficamten Results

Screening

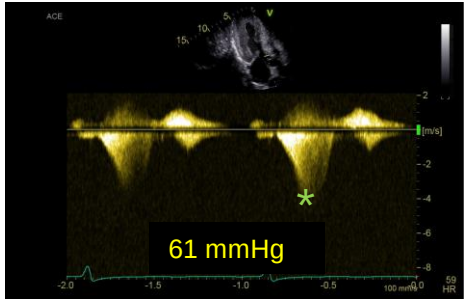
Septal e’



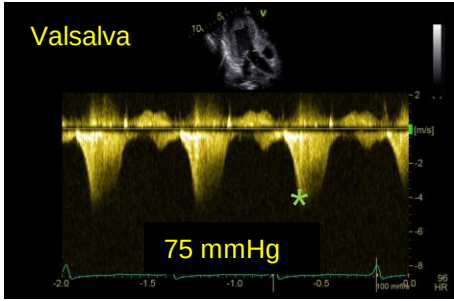
Lateral e’



LVOT Gradient, Rest

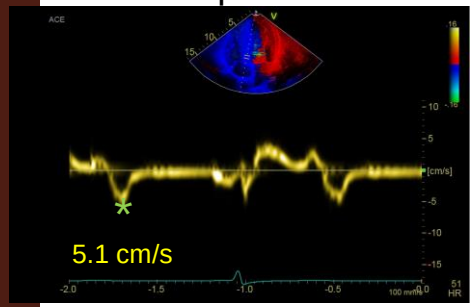


LVOT Gradient, Valsalva

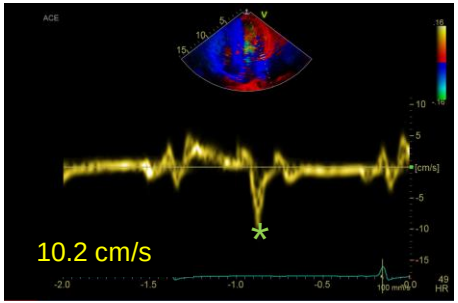


Week 24

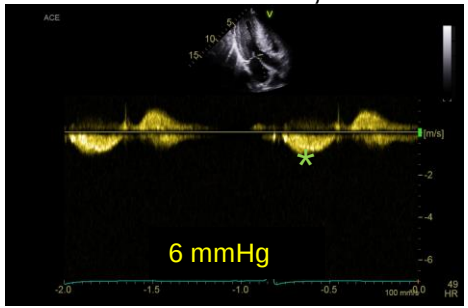
Septal e’



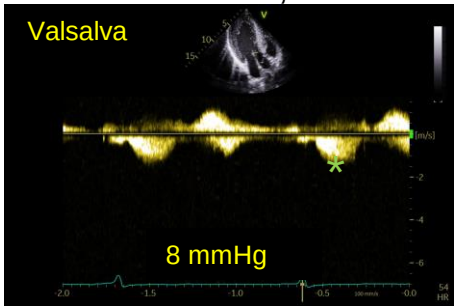
Lateral e’



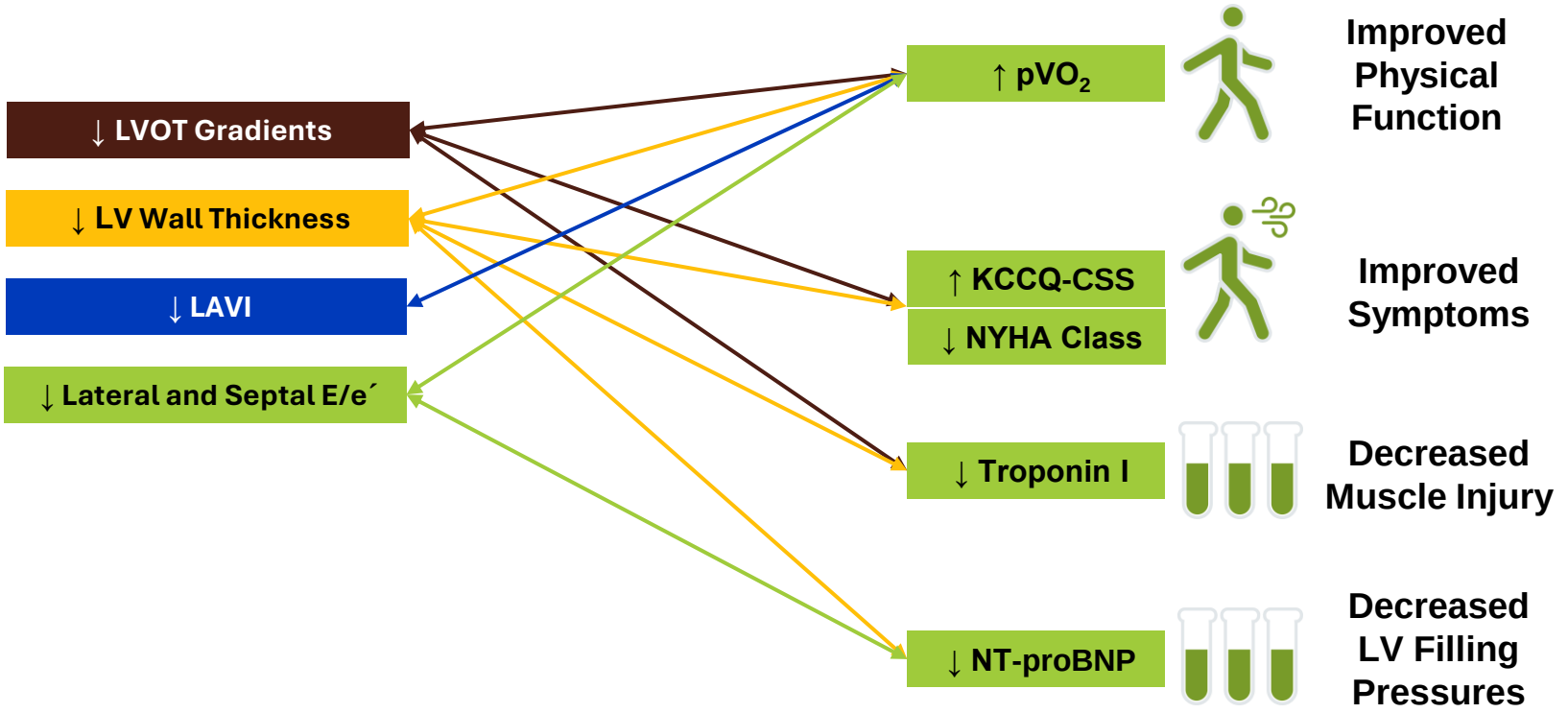
LVOT Gradient, Rest



LVOT Gradient, Valsalva



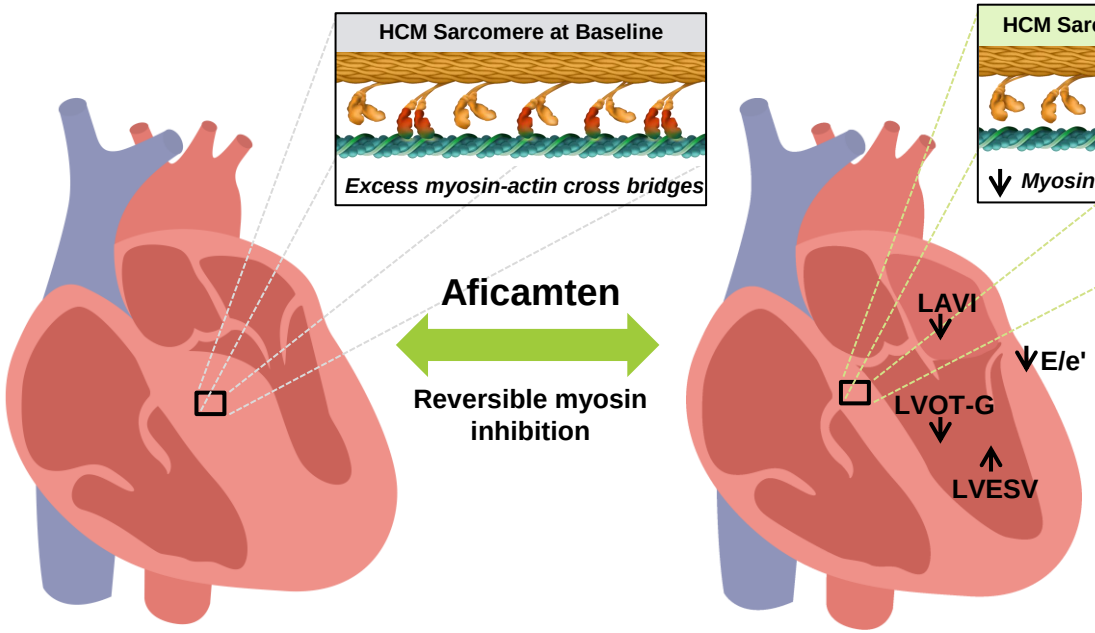
Changes in Echocardiographic Measures are Associated with pVO_2 and Changes in Other Outcomes in Aficamten-treated Patients



Linear regression of change in echo variables associated with change in pVO_2 (mL/kg/min), log_2 NT-proBNP (ng/L), KCCQ-CSS, adjusting for baseline echo variable, baseline outcome variable, beta-blocker use, and exercise mode (bicycle vs treadmill) in aficamten group.

Conclusions

Effect of Aficamten on Cardiac Structure and Function



- ↓ LVOT Gradients
- ↑ LV End Systolic Volume
- ↓ LV Wall Thickness
- Improved LV Diastolic Function
  ↓ LAVI, ↑e´, ↓ E/e´
- Decreased Hypercontractility
  ↓ LVEF, ↓LV GCS

ESV, end systolic volume; GCS, global circumferential strain.

Conclusions

- Aficamten demonstrated significant improvement in measures of LV structure and function.
- Improvement in several of these measures was associated with improvements in pVO_2, KCCQ-CSS, NYHA class, NT-proBNP, and high-sensitivity troponin I.
- A modest decline in measures of LV systolic function occurred (LVEF, LV GCS), yet they remained within normal range, reflecting less hypercontractility.
- Several measures, including LVEF, LVOT gradients, and E/e´ returned to baseline following washout.

These findings suggest aficamten improved multiple structural and physiologic parameters in obstructive HCM without significant adverse changes in LV systolic function.

Future Directions

REDWOOD HCM

Phase 2

SEQUOIA HCM

Phase 3

Open-label extension

FOREST HCM

Acknowledgements

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We thank the following individuals for their contributions to this clinical trial:

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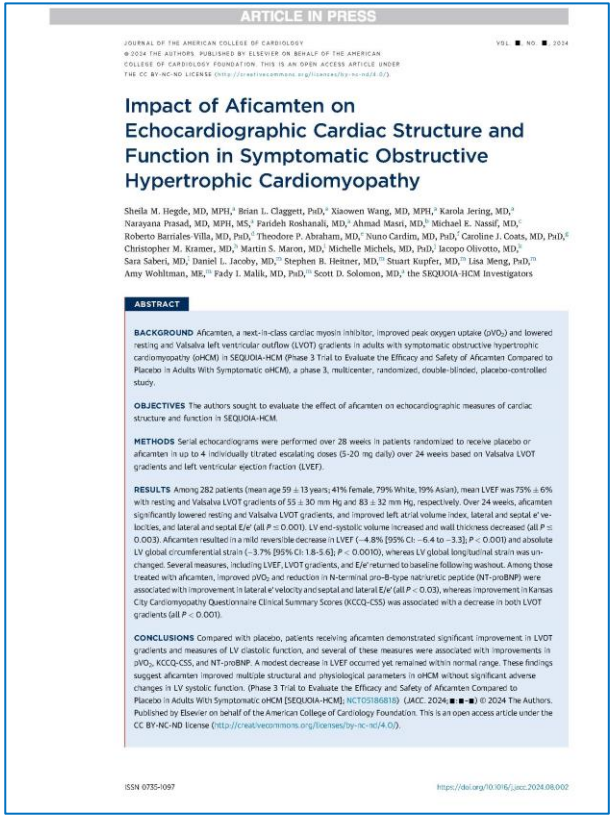
- Investigators and study site staff
- Brigham and Women's Hospital Cardiovascular Imaging Core Laboratory
- Data Monitoring Committee members
- Steering Committee members: Gregory D. Lewis, Theodore Abraham, Michael Arad, Nuno Cardim, Lubna Choudhury, Caroline J. Coats, Milind Desai, Hans-Dirk Düngen, Pablo Garcia-Pavia, Albert A. Hagège, Carolyn Y. Ho, James L. Januzzi, Christopher Kramer, Raymond Kwong, Matthew M.Y. Lee, Chang-Sheng Ma, Martin S. Maron, Ahmad Masri, Michelle Michels, Iacopo Olivotto, Artur Oreziak, Anjali T. Owens, Sara Saberi, Scott D. Solomon, John A. Spertus, Jacob Tfelt-Hansen, Marion van Sinttruije, Josef Veselka, and Hugh C. Watkins

Simultaneously Published in *JACC*



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Impact of Aficamten on Echocardiographic Cardiac Structure and Function in Symptomatic Obstructive Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND Aficamten, a next-in-class cardiac myosin inhibitor, improved peak oxygen uptake (pVO_2) and lowered resting and Valsalva left ventricular outflow (LVOT) gradients in adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in SEQUOIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM), a phase 3, multicenter, randomized, double-blinded, placebo-controlled study.

OBJECTIVES The authors sought to evaluate the effect of aficamten on echocardiographic measures of cardiac structure and function in SEQUOIA-HCM.

METHODS Serial echocardiograms were performed over 28 weeks in patients randomized to receive placebo or aficamten in up to 4 individually titrated escalating doses (5-20 mg daily) over 24 weeks based on Valsalva LVOT gradients and left ventricular ejection fraction (LVEF).

RESULTS Among 282 patients (mean age 59 ± 13 years; 41% female, 79% White, 19% Asian), mean LVEF was 75% ± 6% with resting and Valsalva LVOT gradients of 55 ± 30 mm Hg and 83 ± 32 mm Hg, respectively. Over 24 weeks, aficamten significantly lowered resting and Valsalva LVOT gradients, and improved left atrial volume index, lateral and septal e' velocities, and lateral and septal E/e' (all $P \leq 0.001$). LV end-systolic volume increased and wall thickness decreased (all $P \leq 0.003$). Aficamten resulted in a mild reversible decrease in LVEF (−4.8% [95% CI: −6.4 to −3.3]; $P < 0.001$) and absolute LV global circumferential strain (−3.7% [95% CI: 1.8-5.6]; $P < 0.0010$), whereas LV global longitudinal strain was unchanged. Several measures, including LVEF, LVOT gradients, and E/e' returned to baseline following washout. Among those treated with aficamten, improved pVO_2 and reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) were associated with improvement in lateral e' velocity and septal and lateral E/e' (all $P < 0.03$), whereas improvement in Kansas City Cardiomyopathy Questionnaire Clinical Summary Scores (KCCQ-CSS) was associated with a decrease in both LVOT gradients (all $P < 0.001$).

CONCLUSIONS Compared with placebo, patients receiving aficamten demonstrated significant improvement in LVOT gradients and measures of LV diastolic function, and several of these measures were associated with improvements in pVO_2, KCCQ-CSS, and NT-proBNP. A modest decrease in LVEF occurred yet remained within normal range. These findings suggest aficamten improved multiple structural and physiological parameters in oHCM without significant adverse changes in LV systolic function. (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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