Effect of Aficamten on Cardiac Structure and Function in Patients with Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

Results from the ACACIA-HCM Trial

Sheila M. Hegde[1,2], Xiaowen Wang[2], Scott D. Solomon[2], on behalf of the ACACIA-HCM Investigators

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Background (I)

- Limited proven therapies are available for patients with symptomatic nonobstructive HCM (nHCM)
- Symptom burden in nHCM has been attributed to diastolic dysfunction, impaired myocardial energetics, microvascular ischemia, and myocardial fibrosis
- Aficamten, a next-in-class cardiac myosin inhibitor approved for use in patients with obstructive HCM, improved symptoms and exercise capacity with improvement in LVOT gradients, diastolic function, and mitral regurgitation.

LVOT, left ventricular outflow tract.

Background (II)

- In the phase 3, randomized, placebo-controlled ACACIA-HCM trial, aficamten also significantly improved both symptoms and exercise capacity in patients with symptomatic nHCM.[1]

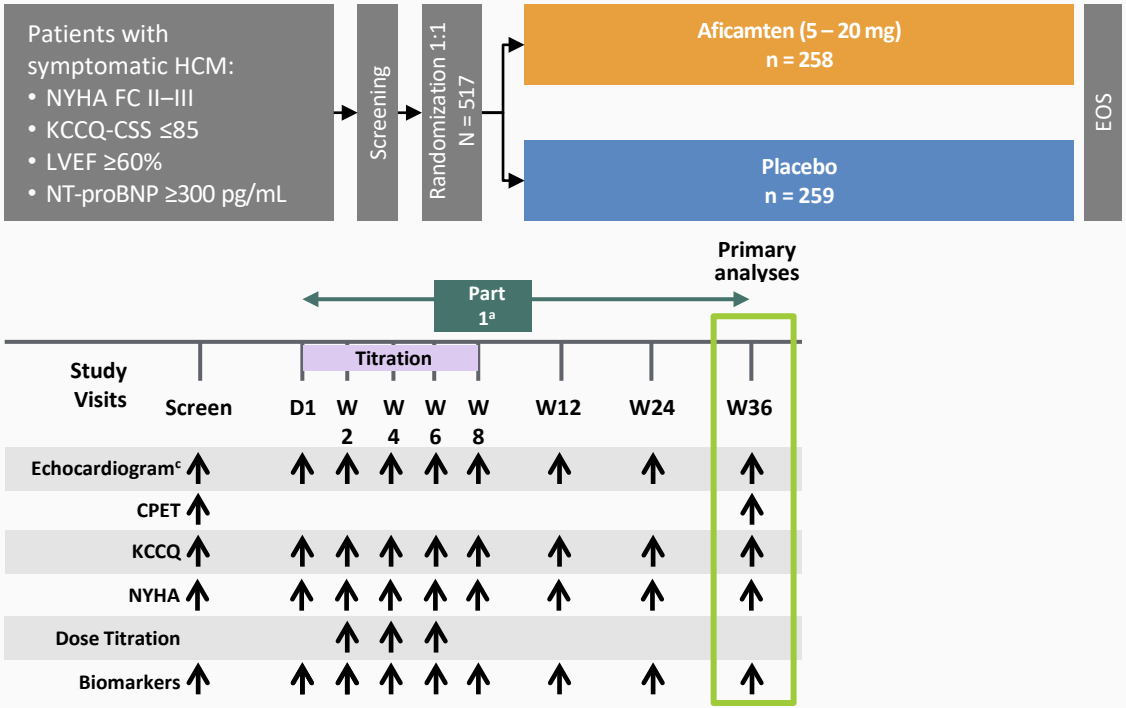
- This pre-specified exploratory analysis evaluated the effect of aficamten on cardiac structure and function in patients with nHCM and may provide insights into the mechanisms responsible for the therapeutic effect of aficamten in the absence of LVOT obstruction.

KCCQ-CSS	peak VO_2
LSM Difference: +3.0 (*P*=0.021)	**LSM Difference: +0.67 mL/kg/min (*P*=0.003)**

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LSM, least squares mean; LVOT, left volume outflow tract; nHCM, nonobstructive cardiomyopathy; peak VO_2,peak oxygen consumption

1. Masri A, et al. *N Engl J Med*. In press.

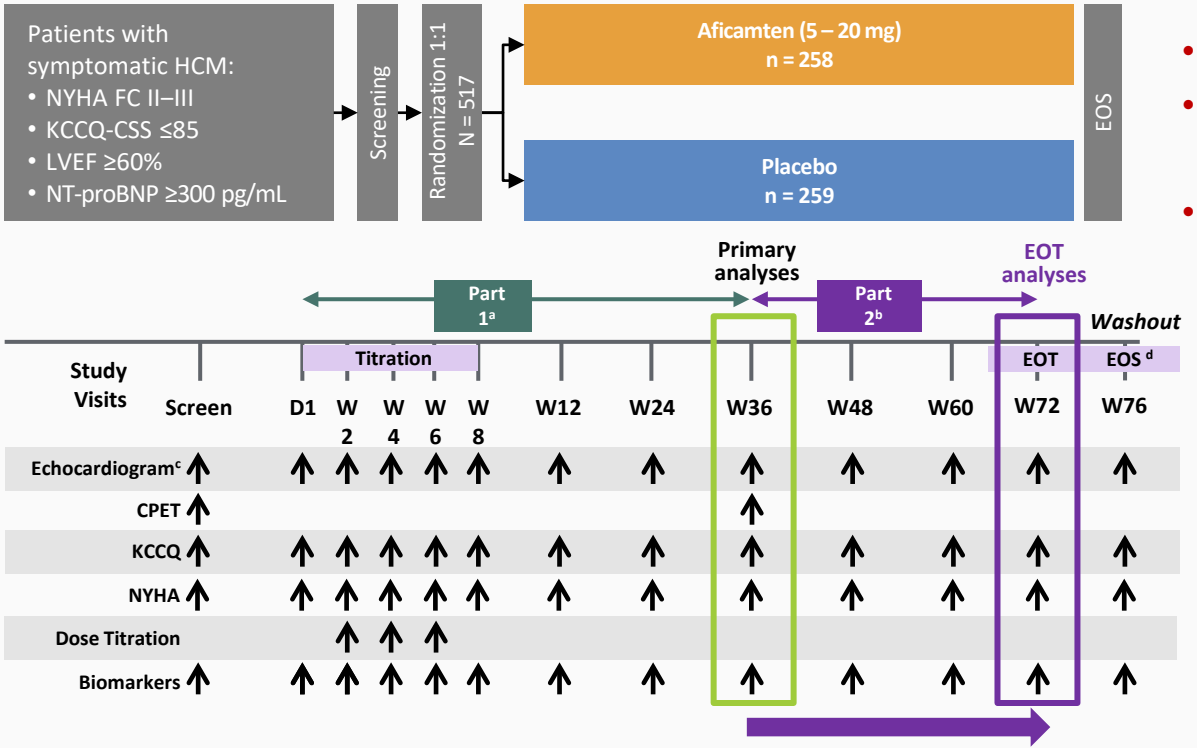
Methods: Study Design



- Dose range: 5 to 20 mg.
- Titration by LVEF through Week 6.
- Prespecified Exploratory Analysis:
  - At 36 weeks.

[a] Part 1: All patients followed until W36.
[b] Part 2: When ≥200 patients reached 52 weeks of treatment, all remaining active study patients who completed W36 were eligible for an EOT visit followed by an EOS visit.
[c] Site-read focused echocardiogram for titration visit (sole criterion).
[d] Occurred ≥4 weeks after the last dose of investigational product.
AF, atrial fibrillation; CPET, cardiopulmonary exercise testing; D, day; EOS, end of study; EOT, end of treatment; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; nHCM, nonobstructive hypertrophic cardiomyopathy; NYHA, New York Heart Association; W, week

Methods: Study Design



- Dose range: 5 to 20 mg.
- Titration by LVEF through Week 6.

- Prespecified Exploratory Analysis:
  - At 36 weeks.
  - At EoT (up to 72 weeks):
    - Median time: 49 weeks [43–61] n=471 to 476.
    - Most recent available data from Week 36 going forward.

Linear regression adjusted for baseline values, intracavity obstruction, and baseline permanent AF

[a] Part 1: All patients followed until W36.
[b] Part 2: When ≥200 patients reached 52 weeks of treatment, all remaining active study patients who completed W36 were eligible for an EOT visit followed by an EOS visit.
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Results: Baseline Characteristics

Characteristic	Aficamten (n=258)	Placebo (n=259)
Age, years	56 ±16	55 ±16
Female sex	140 (54)	137 (53)
Race		
White	200 (78)	188 (73)
Asian	30 (12)	39 (15)
Black	17 (7)	16 (6)
Other	28 (11)	32 (12)
Medical History		
Hypertension	102 (40)	101 (39)
Pathogenic/likely pathogenic sarcomere variant	124/197 (63)	107/193 (55)
Paroxysmal atrial fibrillation or atrial flutter	78 (30)	68 (26)
Permanent/persistent atrial fibrillation	20 (8)	19 (7)
Background HCM therapy		
Beta-blocker	203 (79)	197 (76)
Nondihydropyridine Calcium channel blocker	31 (12)	39 (15)
None	34 (13)	42 (16)
Implantable cardioverter-defibrillator	107 (42)	105 (41)
KCCQ-CSS	66 ±16	65 ±15
NYHA classification		
II / III	171 (66) / 84 (32)	183 (71) / 74 (29)
pVO_2, mL/kg/min	18.0 ± 5.3	18.0 ± 5.1

- Mean Age: 55 ± 16 years
- Female Sex: 54%
- Race: 75% White, 13% Asian

- Paroxysmal AF: 28%
- Permanent AF: 8%
- Beta-blocker use: 77%

- Mean KCCQ-CSS: 66 ± 16
- NYHA class (II/III): 68%/31%
- Mean pVO_2: 18.0 ± 5.2

- Intracavity obstruction: 47 (9%)

AF, atrial fibrillation or atrial flutter; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; NYHA, New York Heart Association; pVO_2,peak oxygen consumption

Results: Baseline Echo Characteristics

Characteristic	Aficamten (n=258)	Placebo (n=259)
LV Structure and Function	68 ± 4	68 ± 3
LVEF, %	68 ± 4	68 ± 3
Maximal wall thickness, cm	2.2 ± 0.5	2.3 ± 0.6
LV end-diastolic volume index, mL/m^2	35.4 ± 7.2	34.6 ± 7.0
LV end-systolic volume index, mL/m^2	11.4 ± 3.2	11.0 ± 2.7
LAVI, mL/m^2	36.8 ± 10.9	37.5 ± 11.9
E/A ratio	1.4 ± 0.8	1.4 ± 0.8
Peak E wave velocity, cm/s	74.5 ± 24.5	70.3 ± 23.7
Peak A wave velocity, cm/s	61.0 ± 27.5	57.3 ± 26.3
Lateral e' velocity, cm/s	7.6 ± 2.5	7.7 ± 2.8
Septal e' velocity, cm/s	5.1 ± 1.7	5.1 ± 1.7
Lateral E/e'	10.7 ± 5.2	10.2 ± 5.1
Septal E/e'	15.9 ± 7.4	14.9 ± 6.7
RV Structure and Function		
RV end diastolic area, cm^2	15.5 ± 3.0	15.4 ± 2.8
RV end systolic area, cm^2	9.4 ± 1.9	9.4 ± 1.8
RV fractional area change, %	39 ± 5	39 ± 5
RV s' velocity, cm/s	12.1 ± 2.7	12.5 ± 2.5
TAPSE, cm	2.1 ± 0.5	2.2 ± 0.4
Peak TR velocity, cm/s	261 ± 39	254 ± 38

- Normal LV systolic function.
- Mean max wall thickness: 2.3 ± 0.5 cm.
- Small LV volumes.
- Mildly dilated LA volumes.
- Abnormal diastolic function.[1]
  - Borderline lateral e' velocities.
  - Reduced septal e' velocities.
  - Indeterminate lateral E/e'.
  - Increased septal E/e'.
- Normal RV structure and function.

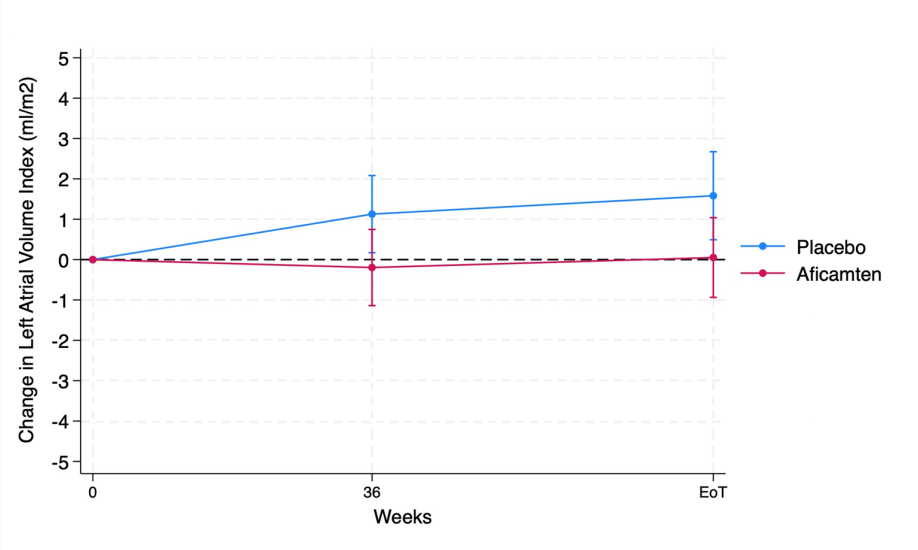
1. Nagueh SF, et al. J Am Soc Echocardiogr. 2025;38:537– 569.

Peak TR velocity was available in a subset (n=234 or 45%)

LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVEF, LV ejection fraction; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Results: Left Atrial Volume Index

Change in Left Atrial Volume Index over Time



Baseline Values:
Aficamten: 38.1 ± 15.1
Placebo: 38.6 ± 13.1

W36
Treatment Effect
−1.3 mL/m^2
(−2.6, 0.04)
P=0.06

EoT
Treatment Effect
−1.7 mL/m^2
(−3.2, −0.3)
P=0.022

Trend towards improvement in LAVI with longer aficamten treatment

↓

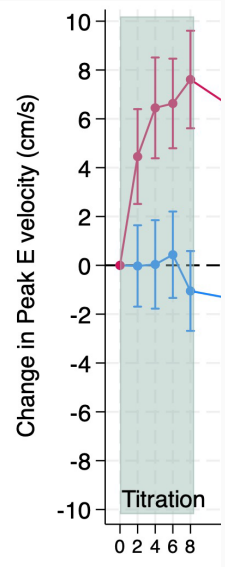
Stabilization of LAVI with aficamten

Analysis excludes those with AF by baseline ECG (n=26)

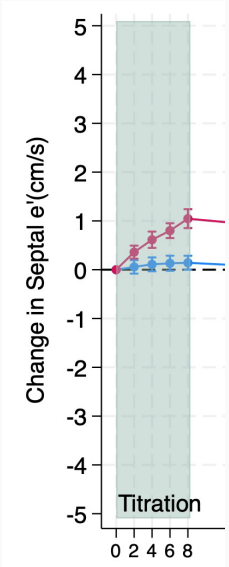
Analysis for LAVI at 36 weeks is the same result and methodology from the primary manuscript accounting for missing data. EoT analysis included the most recent available value and imputed Week 36 for missing data. Treatment effect at EoT assessed by linear regression adjusted for baseline values, intracavity obstruction, and baseline atrial fibrillation.
Patients with atrial fibrillation on baseline ECG were excluded from LAVI analyses. LAVI was not assessed during titration.
AF, atrial fibrillation; ECG, echocardiogram; EOT, end of treatment; LAVI, left atrial volume index, W, Week.

Results: Diastolic Function During Titration

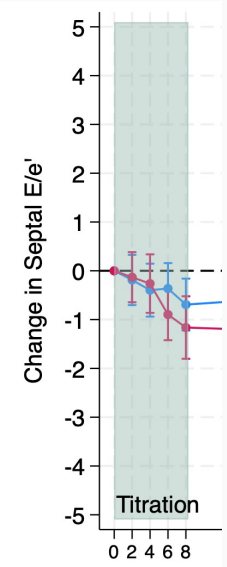
Change in Peak E Velocity over Time



Change in Septal e' Velocity over Time



Change in Septal E/e' over Time

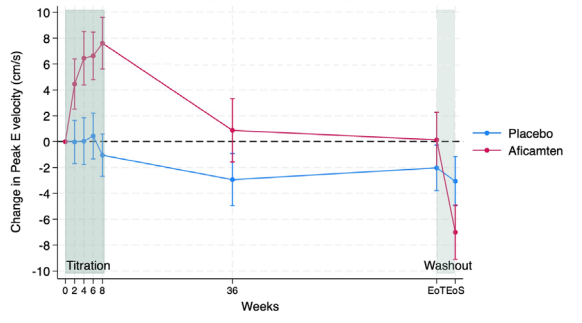


Incremental changes in diastolic function observed with dose titration of aficamten

***Week 8 Aficamten dose**: 0 mg, 5 (2%); 5 mg, 14 (6%); 10 mg, 17 (7%); 15 mg, 60 (24%); 20 mg, 155 (62%)*

Results: Diastolic Function

Change in Peak E Velocity over Time



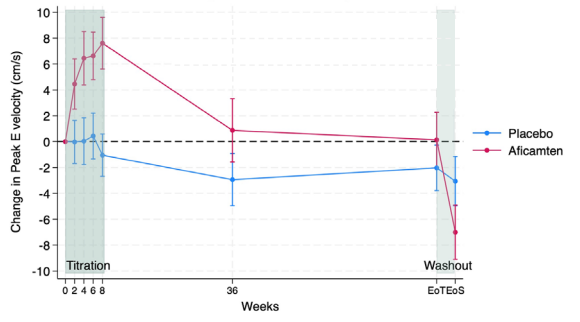
Baseline Values:
Aficamten: 74.5 ± 24.5
Placebo: 70.3 ± 23.7

W36	EoT
Treatment Effect	Treatment Effect
5.1 cm/s (2.2, 8.0)	2.9 cm/s (0.2, 5.5)
P=0.001	*P*=0.034

Treatment effect assessed by linear regression adjusted for baseline values, intracavity obstruction, and baseline atrial fibrillation.
EOT, end of treatment; W, Week.

Results: Diastolic Function

Change in Peak E Velocity over Time



Baseline Values:
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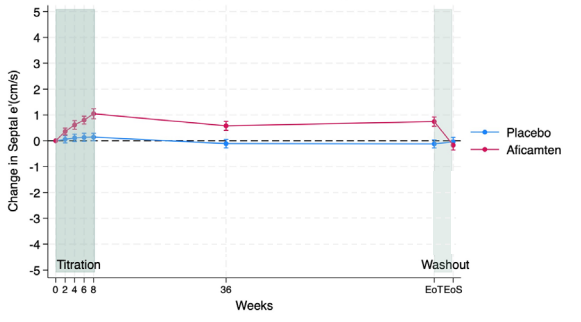
W36 Treatment Effect	EoT Treatment Effect
5.1 cm/s (2.2, 8.0)	2.9 cm/s (0.2, 5.5)
P=0.001	*P*=0.034

Change in Septal e' Velocity over Time

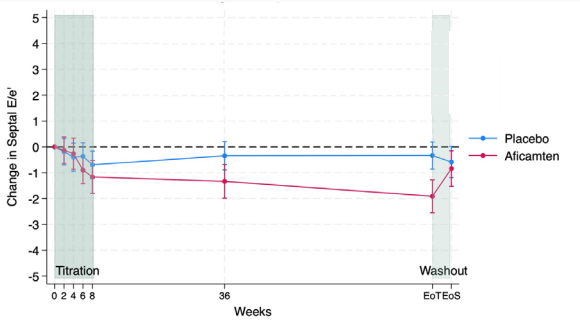


Baseline Values:
Aficamten: 5.1 ± 1.7
Placebo: 5.1 ± 1.7

W36 Treatment Effect	EoT Treatment Effect
0.7 cm/s (0.4, 0.9)	0.9 cm/s (0.6, 1.1)
P<0.001	*P*<0.001

Similar changes observed in lateral e' velocity

Change in Septal E/e' over Time



Baseline Values:
Aficamten: 15.9 ± 7.4
Placebo: 14.9 ± 6.7

W36 Treatment Effect	EoT Treatment Effect
−0.7 (−1.5, 0.1)	−1.4 (−2.1, −0.6)
P=0.07	*P*<0.001

No significant change in Lateral E/e' at Week 36 or EoT

Aficamten improved septal and lateral e' velocities

Trend towards improvement in septal E/e' with longer treatment

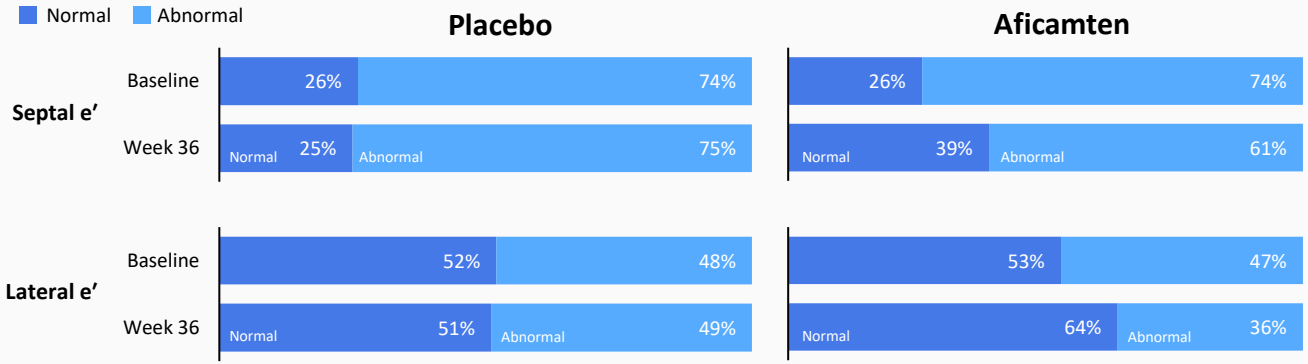
Treatment effect assessed by linear regression adjusted for baseline values, intracavity obstruction, and baseline atrial fibrillation.
EOT, end of treatment; W, Week.

Results: Prevalence of Abnormal Diastolic Function Measures

2025 ASE Guidelines abnormal ranges[1]

- Septal e' ≤ 6 cm/s
- Lateral e' ≤ 7 cm/s

- Septal E/e' ≥ 15
- Lateral E/e' ≥ 13



1. Nagueh SF, et al. *J Am Soc Echocardiogr*. 2025;38:537-69.

Results: Prevalence of Abnormal Diastolic Function Measures

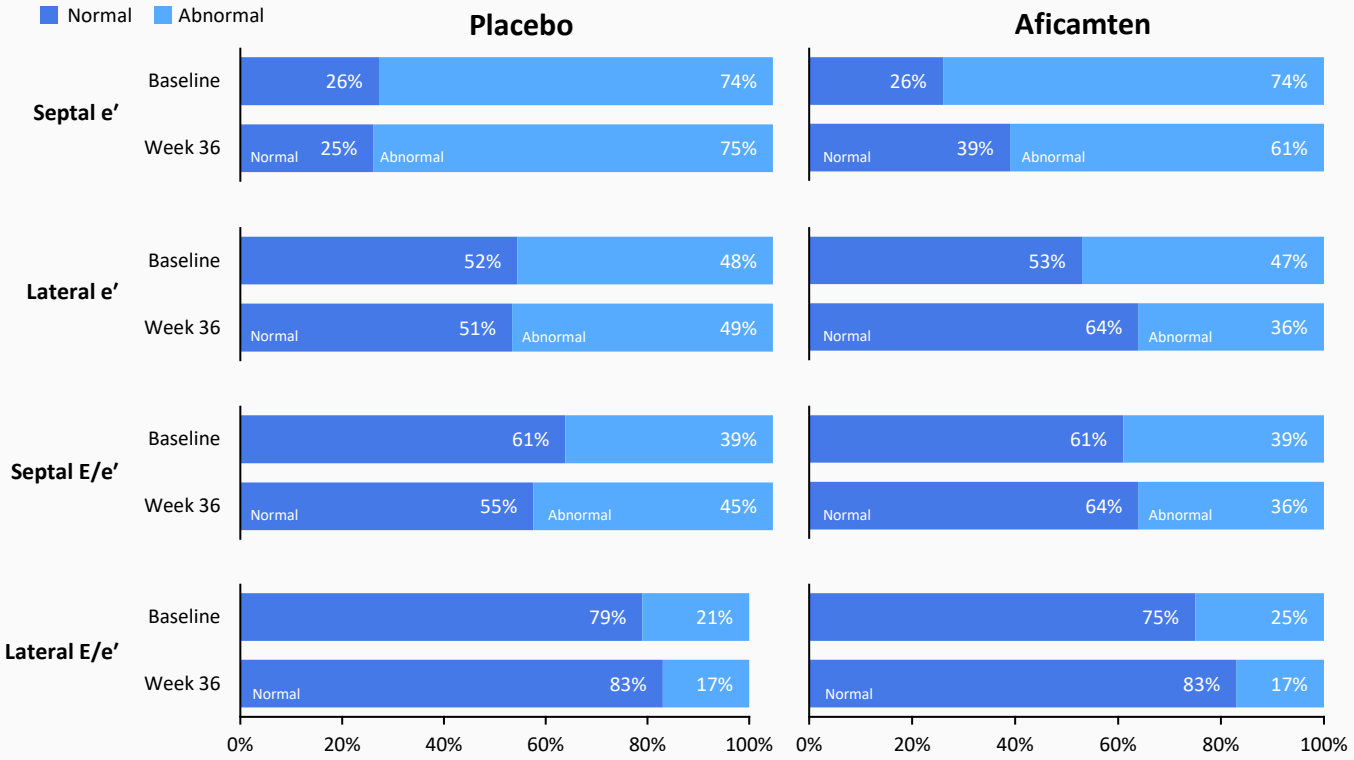
2025 ASE Guidelines abnormal ranges[1]

- Septal e' ≤ 6 cm/s
- Lateral e' ≤ 7 cm/s

- Septal E/e' ≥ 15
- Lateral E/e' ≥ 13

High prevalence of *abnormal* e' velocities with significant improvement with aficamten (septal > lateral)

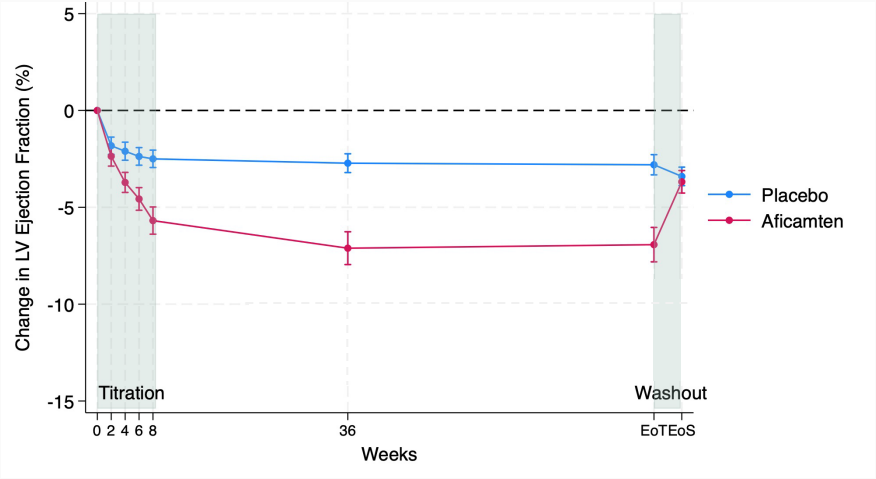
High prevalence of *normal* E/e' with no significant improvement



1. Nagueh SF, et al. *J Am Soc Echocardiogr*. 2025;38:537-69.

Results: LV Systolic Function and LV Wall Thickness

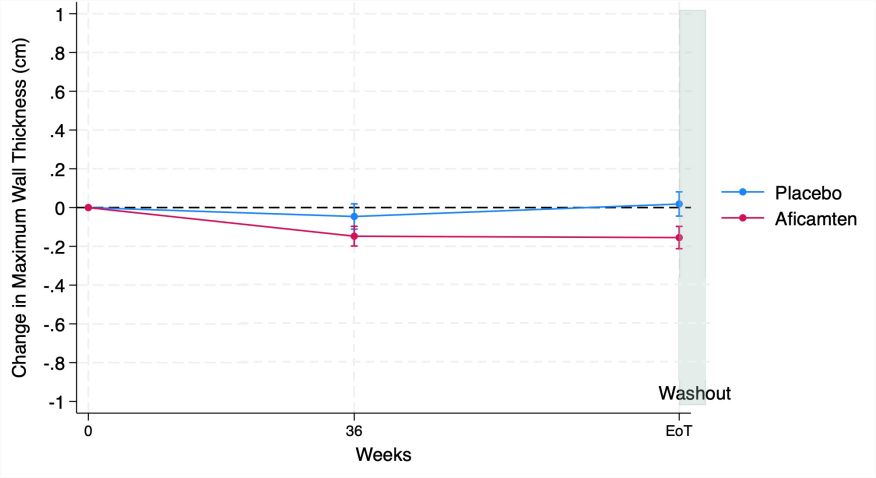
Change in Left Ventricular Ejection Fraction over Time



Baseline Values:
Aficamten: 68 ± 4
Placebo: 68 ± 3

W36 Treatment Effect	EoT Treatment Effect
−4.6% (−5.5, −3.6)	−4.4% (−5.3, −3.4)
P<0.001	*P*<0.001

Change in Maximum Wall Thickness over Time



Baseline Values:
Aficamten: 2.2 ± 0.5
Placebo: 2.3 ± 0.6

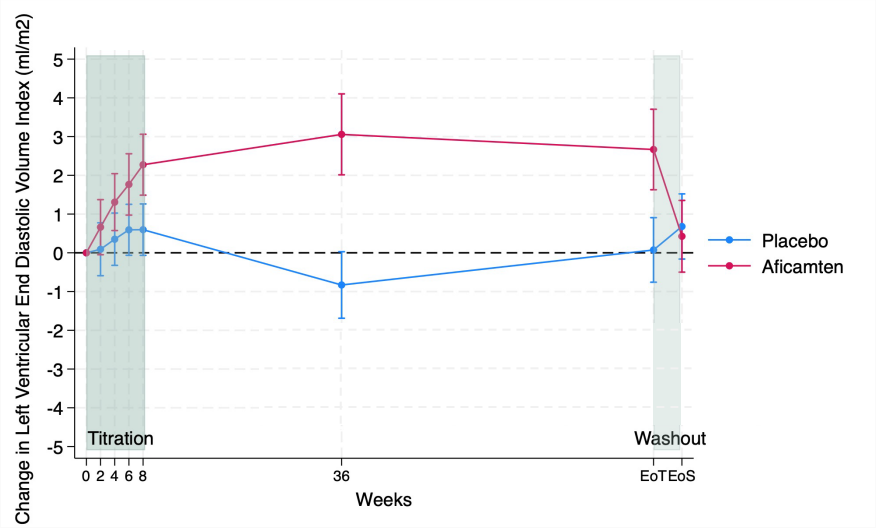
W36 Treatment Effect	EoT Treatment Effect
−0.13 cm (−0.20, −0.07)	−0.20 cm (−0.27, −0.12)
P<0.001	*P*<0.001

Modest decline in LVEF and maximum wall thickness with aficamten

Treatment effect assessed by linear regression adjusted for baseline values, intracavity obstruction, and baseline atrial fibrillation.
EOT, end of treatment; LVEF, left ventricular ejection fraction; W, Week.

Results: LV Volumes

Change in Left Ventricular End-Diastolic Volume Index

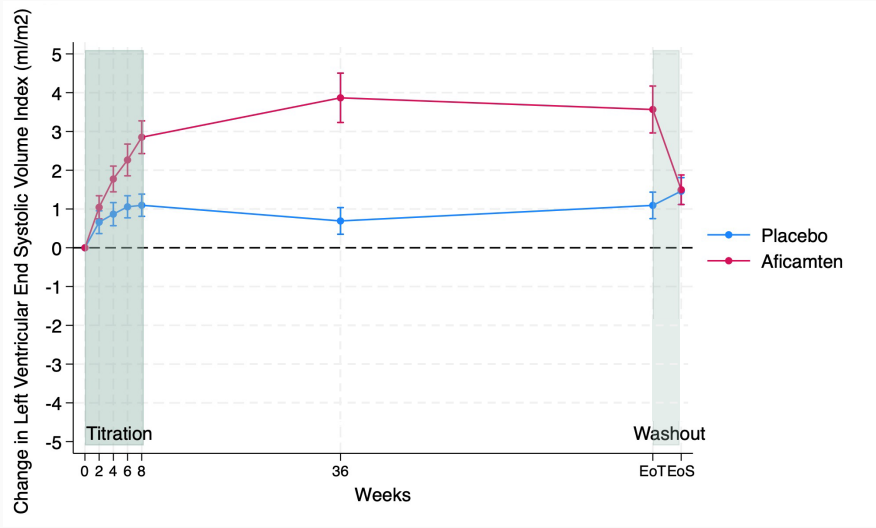


Baseline Values:
Aficamten: 35.4 ± 7.2
Placebo: 34.6 ± 7.0

W36
Treatment Effect
4.1 mL/m^2 (2.8, 5.4)
P<0.001

EoT
Treatment Effect
3.2 mL/m^2 (1.9, 4.5)
P<0.001

Change in Left Ventricular End-Systolic Volume Index



Baseline Values:
Aficamten: 11.4 ± 3.2
Placebo: 11.0 ± 2.7

W36
Treatment Effect
3.2 mL/m^2 (2.5, 4.0)
P<0.001

EoT
Treatment Effect
2.8 mL/m^2 (2.1, 3.6)
P<0.001

Modest increase in LV volumes with aficamten

Treatment effect assessed by linear regression adjusted for baseline values, intracavity obstruction, and baseline atrial fibrillation.
EOS, end of study; EOT, end of treatment; LV, left ventricle.

Results: RV Size and Function

- Modest changes seen in RV structure and function with aficamten:
  - Increase in RV volumes.
  - Decline in TAPSE.
  - Decline in RV s' velocity.
  - Decline in peak TR velocity.

- Persistent changes with longer treatment.

RV Structure	RV Function	RV Hemodynamics
RVEDA 1.0 mL/m^2 (0.5, 1.5) *P*<0.001	**RV FAC** −0.5% (−1.6, 0.6) *P*=0.39	**Peak TR Velocity** -10.4 cm/s (-19.9, -1.0) P=0.03
RVESA 0.7 mL/m^2 (0.4, 1.1) *P*<0.001	**TAPSE** -0.10 cm (-0.16, -0.03) p=0.005	
	RV s' −1.1 cm/s (−1.5, −0.8) *P*<0.001	

Treatment effect assessed by linear regression adjusted for baseline values, intracavity obstruction, and baseline atrial fibrillation.
FAC, fractional area change; RV, right ventricle; RVEDA, RV end diastolic area; RVESA, RV end systolic area; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation

Relationship Between Change in Outcomes and Change in Echocardiographic Measures in Aficamten-Treated Patients

pVO_2 (per 1-unit increase)
Septal e' ↑ 0.08 cm/s (0.01, 0.14) *P*=0.022

KCCQ-CSS (per 5-unit increase)
Septal E/e' ↓ −0.22 (−0.42, −0.03) *P*=0.025
Max wall thickness ↓ −0.02 cm (−0.03, −0.01) *P*=0.009

NT-proBNP (per 50% reduction)	
Septal e' ↑ 0.35 cm/s (0.20, 0.50) *P*<0.001	**Septal E/e'** ↓ −1.01 (−1.57, −0.45) *P*<0.001
Lateral e' ↑ 0.25 cm/s (0.01, 0.48) *P*=0.001	**Max wall thickness** ↓ −0.07 cm (−0.12, −0.03) *P*=0.001
LAVI ↓ −1.1 mL/m^2 (−2.0, −0.1) *P*=0.035	

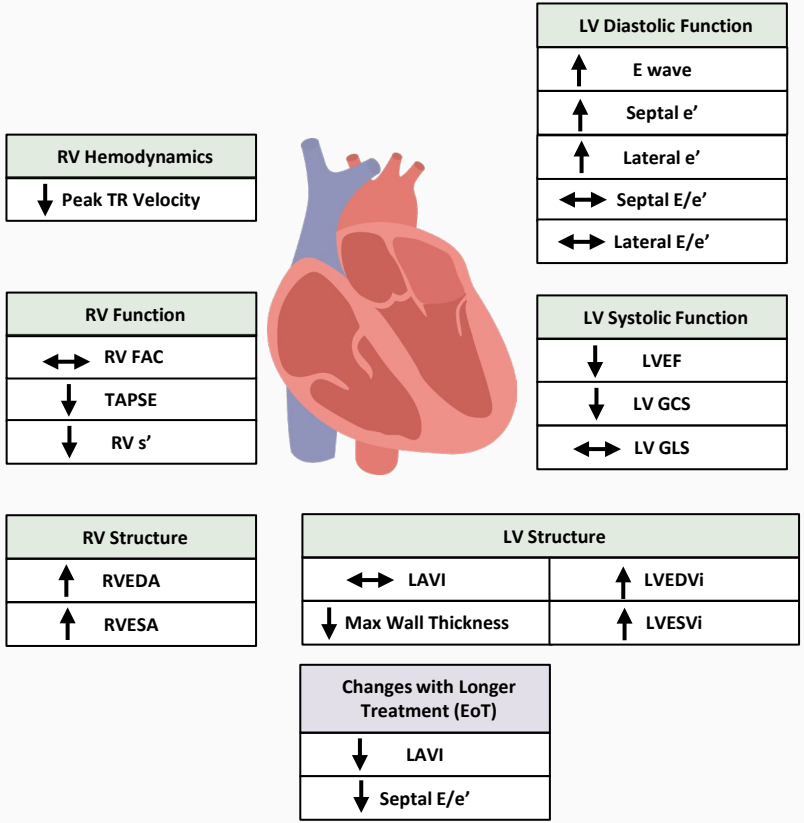
Results assessed at week 36. Other variables assessed and were not significant: LVEF, LVGLS, LVGCS, LV stroke volume, cardiac output, lateral e' velocity, septal e' velocity, lateral E/e', RV FAC, RV s' velocity, TAPSE.

FAC, fractional area change; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LSM, least squares mean; LV, left ventricle; LVEF, LV ejection fraction; LVGLS, LV global longitudinal strain; LVGCS, LV global circumferential strain; pVO_2,peak oxygen consumption; RV right ventricle; TAPSE, tricuspid annular plane systolic excursion

Aficamten in Symptomatic nHCM

- Aficamten demonstrated significant improvement in measures of cardiac structure and function at 36 weeks or with longer treatment.
  - Improvement in measures of diastolic function.
  - Trend towards stabilization of LA size.
  - Modest reduction in LV wall thickness.
- Improvement in pVO_2, KCCQ-CSS, and NT-proBNP was associated with improvement in diastolic function among aficamten treated patients.
- Aficamten resulted in a modest reduction in LV and RV systolic function, yet values remained within normal range.
- There is evidence of reversibility as several measures returned to baseline following washout.

These findings suggest that the benefits of aficamten extend beyond the effects of LV outflow tract gradient reduction observed in prior studies.



FAC, fractional area change; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - Clinical Summary score; LV, left ventricle; NT-proBNP, N-terminal pro–B-type natriuretic peptide; pVO_2, peak oxygen consumption; RV, right ventricle; RVEDA, RV end diastolic area; RVESA, RV end systolic area; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation

Acknowledgments

The ACACIA-HCM trial is funded by Cytokinetics, Incorporated. We thank the following individuals and groups for their contributions to this clinical trial:

- Participants and their families.
- Investigators and study site staff.
- Brigham and Women's Hospital Cardiovascular Imaging Core Laboratory.
- Data Monitoring Committee members.
- Steering Committee members.

Circulation

Effect of Aficamten on Cardiac Structure and Function in Patients with Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

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