Aficamten vs Metoprolol as Monotherapy for Symptomatic Obstructive Hypertrophic Cardiomyopathy

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Dedicated to Lisa Meng, who loved people even more than she loved data (and she loved data immensely).

Disclosures

- Pablo Garcia-Pavia reports speaker fees from Bristol Meyers Squibb, and consulting fees from Alexion, Biomarin, Bristol Meyers Squibb, Cytokinetics, Edgewise Therapeutics, Lexeo Therapeutics, and Rocket Pharmaceuticals.

Background

- Obstructive HCM (oHCM) is characterized by a hypercontractile left ventricle, hypertrophy, and left ventricular outflow tract (LVOT) obstruction, resulting in limiting symptoms and reduced exercise capacity.[1]
- Aficamten is an investigational, next-in-class cardiac myosin inhibitor that targets the underlying pathophysiology of HCM by reducing myocardial hypercontractility.
- When added to patients with oHCM who are symptomatic despite treatment with standard of care, aficamten has been shown to:
  - Increase exercise capacity[2,3]
  - Reduce symptom burden[4]
  - Normalize LVOT gradients[2,5]
  - Reduce the number of patients who are eligible for septal reduction therapy[2]
  - Improve cardiac biomarkers,[6] and cardiac structure and function.[5,7]

1. Maron BJ, et al. N Engl J Med 2018;379:655. **2.** Maron MS, et al. N Engl J Med 2024;390(20):1849. **3.** Lee MMY, et al. JAMA Cardiol 2024;9:990-1100. **4.** Sherrod CF, et al. J Am Coll Cardiol 2024;8(19):1773-85. **5.** Hegde SM, et al. J Am Coll Cardiol 2024;5(19):1789-802. **6**. Coats, CJ, et al. Eur Heart J 2024;8(45):4464-78. **7.** Masri A. et al. J Am Coll Cardiol 2024;84(19):1806-17.

HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract.

Beta-blockers have been the first-line treatment for symptomatic oHCM for nearly 60 years despite limited evidence

1968

Chronic Beta Adrenergic Receptor Blockade in the Treatment of Idiopathic Hypertrophic Subaortic Stenosis[1]

By Lawrence S. Cohen and Eugene Braunwald

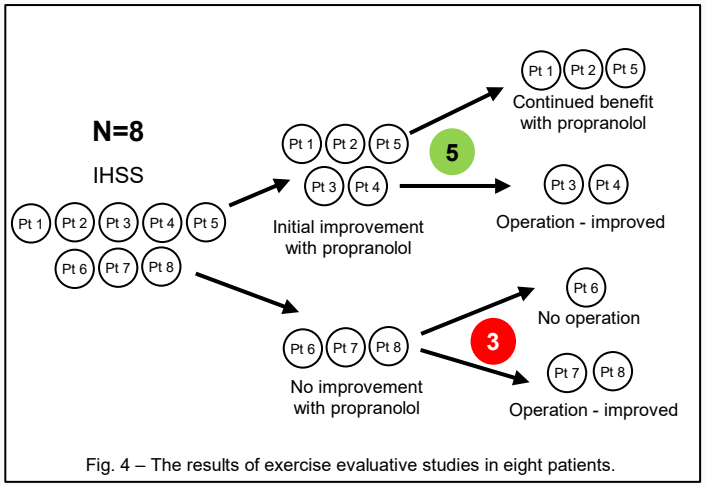


Fig. 4 – The results of exercise evaluative studies in eight patients.

***P*=0.73**

2023 ESC Guidelines[2]

Recommendation	Class[a]	Level[b]
Non-vasodilating beta-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provoked[c] LVOTO.	I	B

[a] Class of recommendation; [b] Level of evidence; [c] Provocation with Valsalva maneuver, upright exercise, or oral nitrates if unable to exercise.

2024 ACC/AHA Guidelines[3]

COR	LOE	Recommendations
1	B-NR	1. In patients with obstructive HCM and symptoms[d] attributable to LVOTO, non-vasodilating beta-blockers, titrated to effectiveness or maximally tolerated doses, are recommended.

[d] Symptoms include effort-related dyspnea or chest pain and occasionally other exertional symptoms (eg, syncope, near syncope) that are attributed to LVOTO and interfere with everyday activity or quality of life.

1. Cohen LS, Braunwald E. Prog Cardiovasc Dis 1968;11:211-21. **2.** Arbelo E, et al. Eur Heart J 2023;44:3503-626. **3.** Ommen SR, et al. Circulation 2024;149:e1239-e1311.

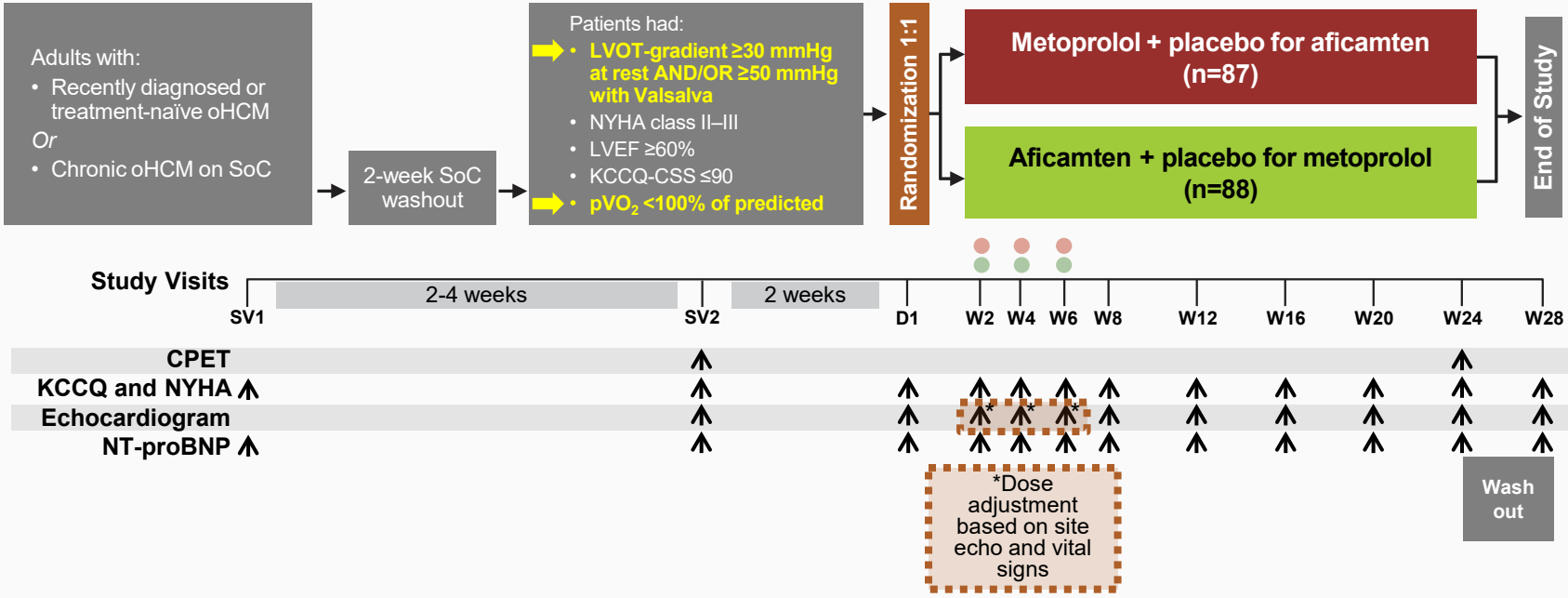
COR, class of recommendation; IHHS, idiopathic hypertrophic subaortic stenosis; LOE, level of evidence; LVOTO, left ventricular outflow tract obstruction; NR, non-randomized.

MAPLE-HCM: Objectives and Endpoints

- Evaluate the safety and efficacy of **aficamten monotherapy compared with metoprolol monotherapy** in patients with symptomatic oHCM.
- **Primary Endpoint:**
  - Exercise capacity (pVO_2)
- **Secondary Endpoints:**
  - Symptoms (NYHA Functional Class and KCCQ-CSS)
  - Valsalva LVOT gradient
  - Biomarkers (NT-proBNP)
  - Cardiac structure and function by echo (LAVI, LVMI)

KCCQ, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LAVI, left atrial volume index; LVOT, left ventricular outflow tract; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen uptake.

MAPLE-HCM: Study design



* Metoprolol doses were uptitrated in 50 mg increments from 50 to 200 mg. Aficamten doses were uptitrated in 5 mg increments from 5 to 20 mg.

CPET, cardiopulmonary exercise testing; D, day; echo, echocardiogram; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake; SoC, standard of care; SV, screening visit; W, week.

Garcia-Pavia P, et al. JACC Heart Fail 2025;13:346-57.

Results: Baseline characteristics

Patients had milder oHCM disease phenotype by design than was previously studied in SEQUOIA-HCM

Characteristic	Aficamten (n=88)	Metoprolol (n=87)
Age, y	58.9 ±13	56.5 ±13
Female sex	36 (40.9)	37 (42.5)
White race	70 (79.5)	70 (80.5)
Geographic region		
China	11 (12.5)	11 (12.6)
North America	45 (51.1)	39 (44.8)
Europe, Israel, and Brazil	32 (36.4)	37 (42.5)
Medical history		
Pathogenic sarcomeric variant[a]	27 (30.7)	22 (25.3)
Hypertension	54 (61.4)	33 (37.9)
HCM therapy at screening[b]		
Beta-blocker	64 (72.7)	59 (67.8)
Calcium channel blocker	12 (13.6)	10 (11.5)
None	19 (21.6)	23 (26.4)
Required washout of SoC	69 (78.4)	64 (73.6)
Recently diagnosed[c]	26 (29.5)	27 (31.0)

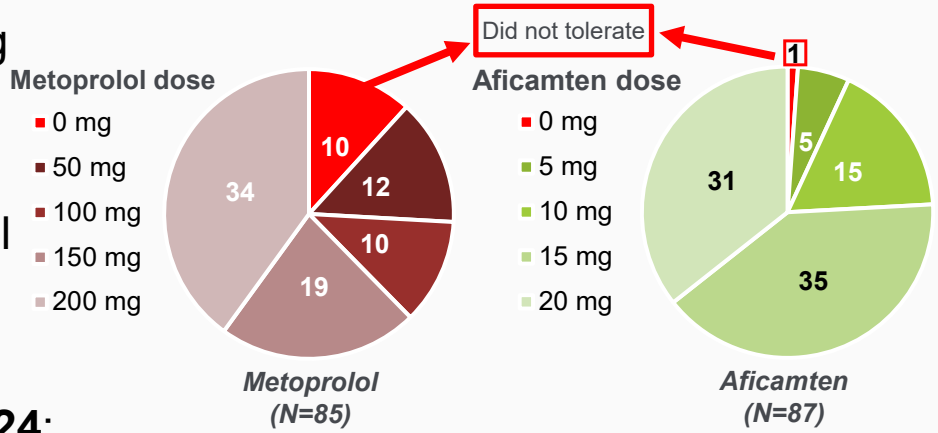
Values are n (%), mean ±SD, or median [IQR]. Percentages may not total 100 because of rounding.

Characteristic	Aficamten (n=88)	Metoprolol (n=87)
KCCQ-CSS	65.5 ±17	66.0 ±16
NYHA FC		
II	63 (72)	60 (69)
III	25 (28)	27 (31)
NT-proBNP, pg/mL	510 [213, 993]	439 [171, 907]
hs-cTnI, ng/L	14.2 [7.3, 34.0]	11.6 [6.3, 25.1]
CPET		
pVO_2, mL/kg/min	19.5 ±4.8	20.2 ±5.3
Percent of predicted pVO_2, %	60.0 ±13.5	61.2 ±13.7
Treadmill	52 (59.1)	52 (59.8)
Echocardiographic parameters		
LVEF, %	68.3 ±3.8	67.3 ±3.9
Valsalva LVOT gradient, mmHg	75.3 ±34.0	71.6 ±31.2
Resting LVOT gradient, mmHg	48.6 ±30.1	46.2 ±27.4
Maximal wall thickness, mm	20.9 ±2.8	20.8 ±3.3
LA volume Index, mL/m^2	37.8 (10.9)	40.1 (12.1)
LV mass index, g/m^2	128.9 (31.6)	133.3 (31.3)

[a] Genetic testing required separate consent and was not performed in 37 patients (n=18 aficamten, n=19 metoprolol). [b] Background SoC medications taken at time of initial screening, before screening washout. [c] Patients who were diagnosed within a year from screening or treatment-naïve.
CPET, cardiopulmonary exercise testing; HCM, hypertrophic cardiomyopathy; hs-cTnI, high sensitivity cardiac troponin I; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen uptake; SoC, standard of care.

Results: Doses achieved

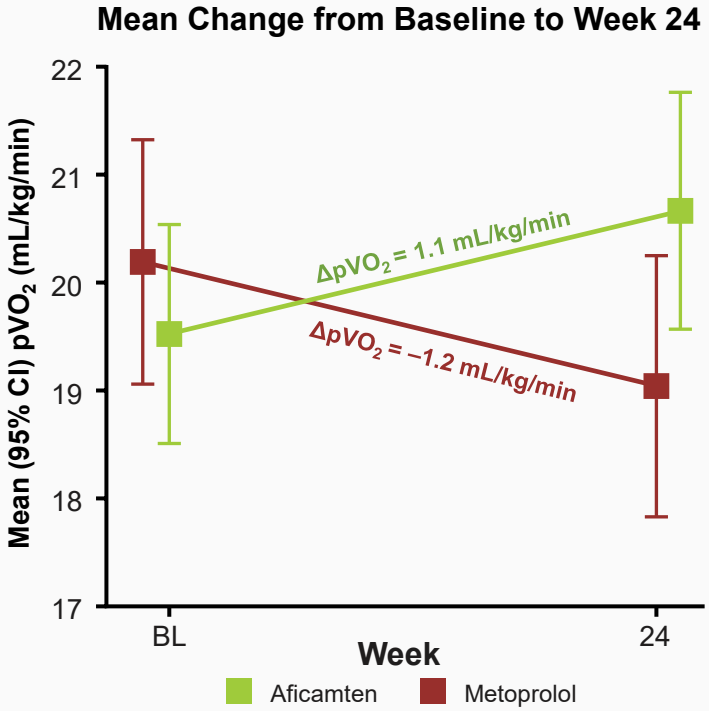
- **The majority of patients were exposed to the highest doses**:
  - Metoprolol: 62% received 150 or 200 mg
  - Aficamten: 76% received 15 or 20 mg
- **At Week 24**:
  - 10 patients did not tolerate metoprolol
  - 1 patient did not tolerate aficamten



- **Pharmacodynamic changes at Week 24**:
  - HR: Metoprolol mean decrease of 6 bpm. Aficamten mean change of −0.2 bpm
  - SBP: Metoprolol mean decrease of 6 mmHg. Aficamten mean increase of 5 mmHg

HR, heart rate; SBP, systolic blood pressure.

Results: Primary endpoint – change in pVO_2



LSM difference (SE) vs metoprolol

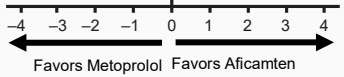
2.3 (0.39) mL/kg/min

***P*<0.0001**

Δ, change; BL, baseline; LSM, least squares mean; pVO_2, peak oxygen uptake; SE, standard error.

Results: Pre-specified subgroups show no heterogeneity in pVO_2

	Aficamten	Metoprolol	LSM Difference (95% CI) in pVO_2
	no. of patients		
Overall	88	87	2.3 (1.52, 3.07)
Gender			
Male	52	50	2.18 (1.2, 3.16)
Female	36	37	2.16 (0.99, 3.33)
Age Group			
< 65 Years	50	61	2.29 (1.31, 3.26)
≥ 65 Years	38	26	2.43 (1.09, 3.76)
Baseline BMI			
< 30 kg/m^2	57	59	2.53 (1.6, 3.47)
≥ 30 kg/m^2	31	28	1.95 (0.62, 3.28)
Baseline NYHA Functional Class			
NYH A Class II	63	60	2.23 (1.3, 3.15)
NYH A Class III	25	27	2.48 (1.03, 3.92)
Baseline LVEF			
≤ Median (68.5%)	39	50	2.65 (1.55, 3.75)
> Median (68.5%)	49	37	1.92 (0.79, 3.06)
Baseline NT-proBNP			
≤ Median (468.0 pg/mL)	41	47	3.04 (1.96, 4.12)
> Median (468.0 pg/mL)	47	40	1.59 (0.50, 2.69)
CPET Modality			
Treadmill	52	52	2.53 (1.52, 3.53)
Bicycle	36	35	1.96 (0.74, 3.18)
Baseline pVO_2			
≤ Median (19.75 mL/kg/min)	49	39	2.54 (1.44, 3.65)
> Median (19.75 mL/kg/min)	39	48	1.95 (0.86, 3.04)
Diagnosis Period			
Diagnosed Recently	26	27	3.22 (1.81, 4.64)
Chronic oHCM	62	60	1.87 (0.95, 2.79)
Baseline Valsalva LVOT gradient			
≤ Median (72.0 mmHg)	44	44	2.32 (1.24, 3.4)
> Median (72.0 mmHg)	44	42	2.3 (1.2, 3.39)
Baseline KCCQ-CSS			
≤ Median (67.7)	42	45	2.29 (1.19, 3.39)
> Median (67.7)	46	42	2.26 (1.14, 3.37)
Sarcomeric Gene Mutation Status			
Positive	27	22	1.94 (0.47, 3.41)
Inconclusive/Negative	43	46	2.36 (1.26, 3.47)



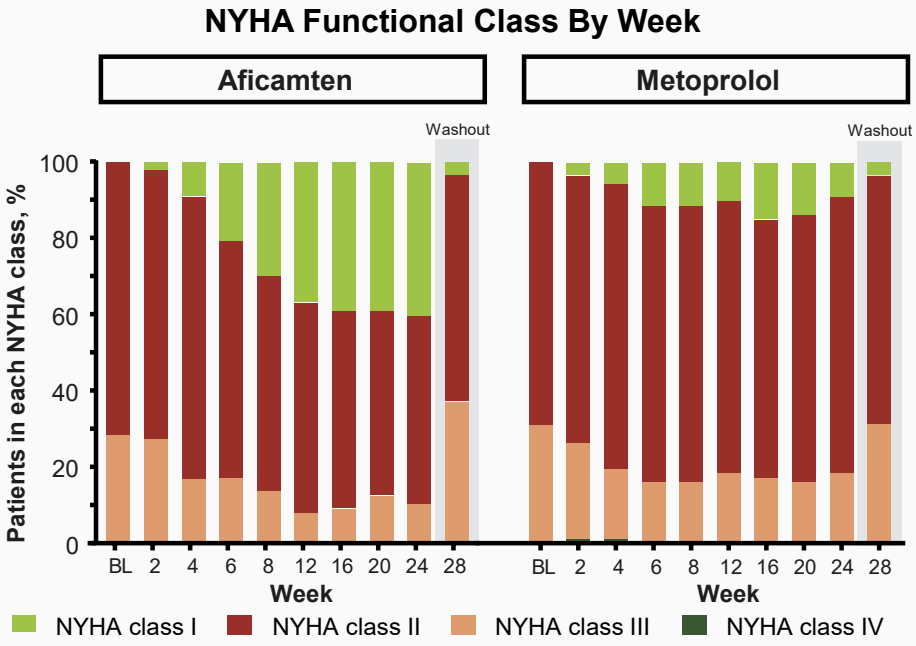
BMI, body mass index; CPET, cardiopulmonary exercise testing; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; LSM, least squares mean; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake.

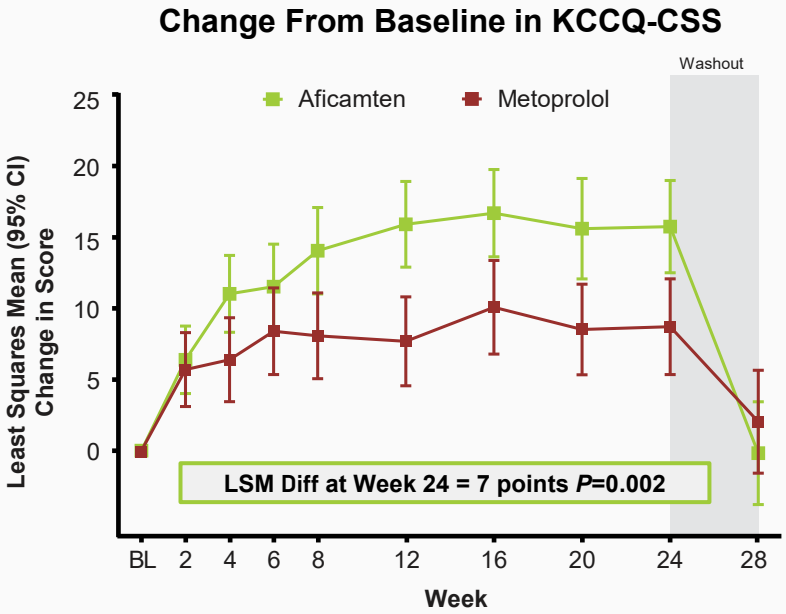
Results: Overview of all secondary endpoints

	Secondary Endpoints	
1	Proportion of patients with ≥1 class improvement in NYHA functional class from baseline to Week 24	*P*<0.001
2	Change in KCCQ-CSS from baseline to Week 24	*P*<0.002
3	Change in NT-proBNP from baseline to Week 24	*P*<0.0001
4	Change in post-Valsalva LVOT gradient from baseline to Week 24	*P*<0.0001
5	Change in LAVI from baseline to Week 24	*P*<0.0001
6	Change in LVMI from baseline to Week 24	*P*=0.163

KCCQ, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LAVI, left atrial volume index; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association.

Secondary endpoints: Functional class and symptoms

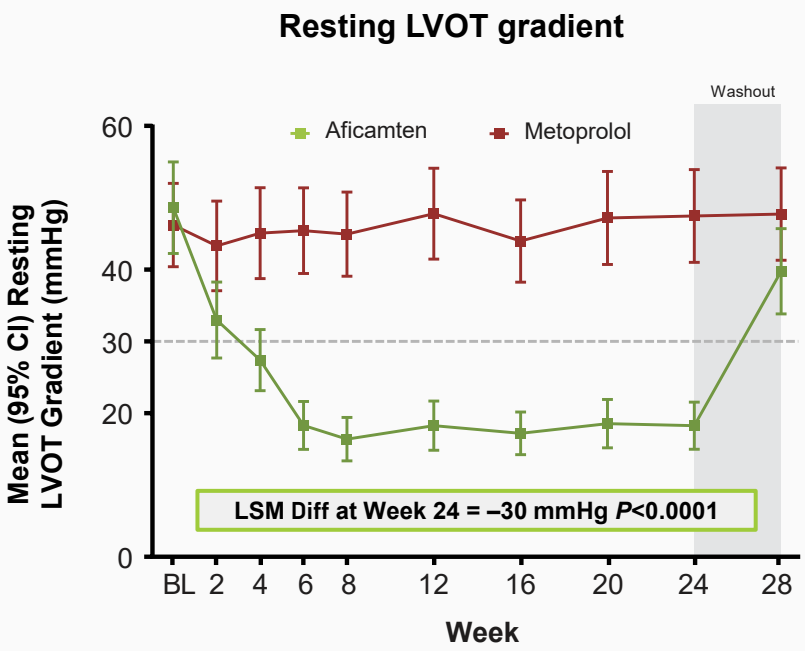


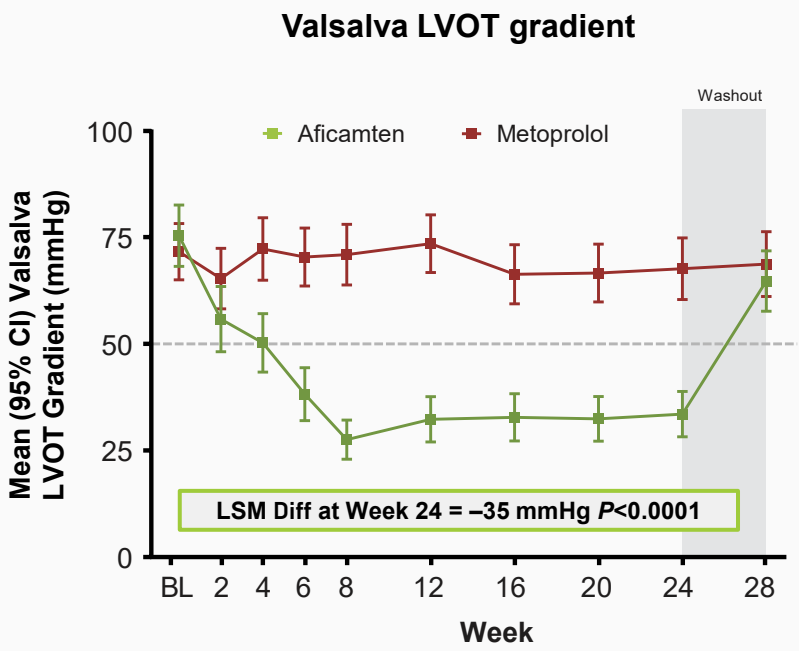


At week 24, 51% of patients treated with aficamten and 26% of patients treated with metoprolol had ≥1 NYHA class improvement, *P*<0.001.

BL, baseline; KCCQ, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LSM, least squares mean; NYHA, New York Heart Association.

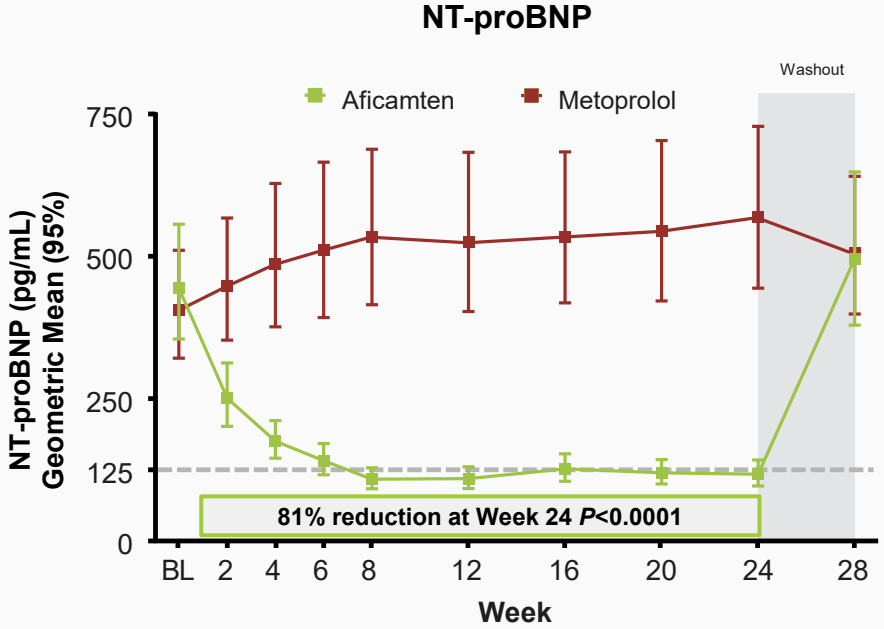
Secondary endpoints: Change in LVOT obstruction at Week 24

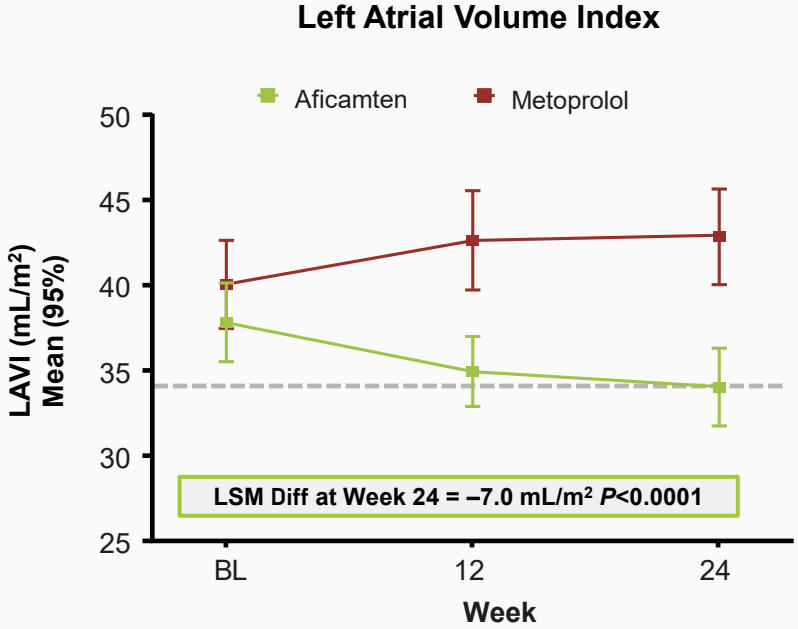




The gray dashed lines indicate the thresholds for resting (30 mmHg; *left panel*) and post-Valsalva (50 mmHg; *right panel*) LVOT gradient for oHCM.
BL, baseline; LSM, least squares mean; LVOT, left ventricular outflow tract; oHCM, obstructive hypertrophic cardiomyopathy.

Secondary endpoints: Change in NT-proBNP and LAVI at Week 24





The gray dashed lines indicate the upper limits of normal: 125 pg/mL (*left panel*) and 34 mL/m^2 (*right panel*).
BL, baseline; LAVI, left atrial volume index; LSM, least squares mean; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

Safety

	Aficamten (n=88)	Metoprolol (n=87)
Patients with any SAE	7 (8.0)	6 (6.9)
Patients with any AE that led to early treatment withdrawal of aficamten or metoprolol[a]	1 (1.1)	3 (3.4)
Patients with AE that led to temporary interruption of aficamten or metoprolol	1 (1.1)	1 (1.1)
Patients with dose reduction due to adverse events	1 (1.1)[b]	4 (4.6)[c]
Patients with ≥1 dose down-titration	4 (4.5)[d]	26 (29.9)[e]
Mean (SD) change in LVEF at Week 24 vs baseline	−5.3% (4.7)	−0.50% (3.7)
LVEF <50% by core lab	1 (1.1)[f]	0

Values are n (%).
[a] In the aficamten group, 1 patient had sudden death after a brief viral illness. In the metoprolol group, AEs leading to early treatment discontinuation are ischemic stroke, hypotension, and fractured humerus due to fall (n=1 each).
[b] In the aficamten group, 1 patient had a dose reduction due to an AE of dizziness.
[c] In the metoprolol group, 4 patients had dose reduction due to AEs of lightheadedness (n=2), bradycardia (n=1), and fatigue (metoprolol, n=1).
[d] In the aficamten group, 3 patients had 4 down-titration events based on site-read LVEF <50% (n=3) and due to an AE (n=1).
[e] In the metoprolol group, 26 patients had 31 down-titration events based on SBP <90 mmHg (n=5), HR <50 bpm (n=17), and AE (n=4).
[f] No associated AE with this LVEF <50%.

AE, adverse event; HR, heart rate; LVEF, left ventricular ejection fraction; SAE, serious adverse event; SBP, systolic blood pressure.

Conclusions

- In patients with symptomatic oHCM, 24 weeks of treatment with **aficamten monotherapy** was **superior to metoprolol monotherapy,** with statistically significant and **clinically meaningful improvements in:**
  - Primary endpoint of exercise capacity (measured by pVO_2).
  - Secondary endpoints of symptoms (NYHA class and KCCQ-CSS), Valsalva LVOT-G, NT-proBNP, and structural remodeling (LAVI).
- Despite strong evidence of on-target hemodynamic effects with metoprolol (HR and SBP), there was no decrease in mean LVOT gradient at rest or with Valsalva.
- **Aficamten** treatment was **well tolerated**.
- These findings support **aficamten monotherapy as the first-line therapy of choice** in patients with symptomatic oHCM.

HR, heart rate; KCCQ, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI, left atrial volume index; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen uptake; SBP, systolic blood pressure.

Acknowledgments

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Steering Committee Members: Pablo Garcia-Pavia (**Co-PI**), Michael Fifer (**Co-PI**), Edileide Correra de Barros, Ozlem Bilen, Melissa Burroughs, Juan Pablo Costabel, Anne Dybro, Perry Elliott, Neal Lakdawala, Amy Mann, Ajith Nair, Michael Nassif, Steen Poulsen, Patricia Reant, Christian Schulze, Andrew Wang

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MAPLE HCM

ORIGINAL ARTICLE

Aficamten or Metoprolol Monotherapy for Obstructive Hypertrophic Cardiomyopathy

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