Aficamten vs Metoprolol Monotherapy in Obstructive Hypertrophic Cardiomyopathy According to Pretrial Treatment in MAPLE-HCM

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Disclosures

- Fernando Dominguez reports speaker fees from Alnylam, Amicus, Bayer, BMS, Cytokinetics, Pfizer, Sanofi, and Takeda and consulting fees from Affinia Therapeutics, Alnylam, Bayer, BMS, Chiesi, Cytokinetics, Lexeo, Pfizer, and Takeda.

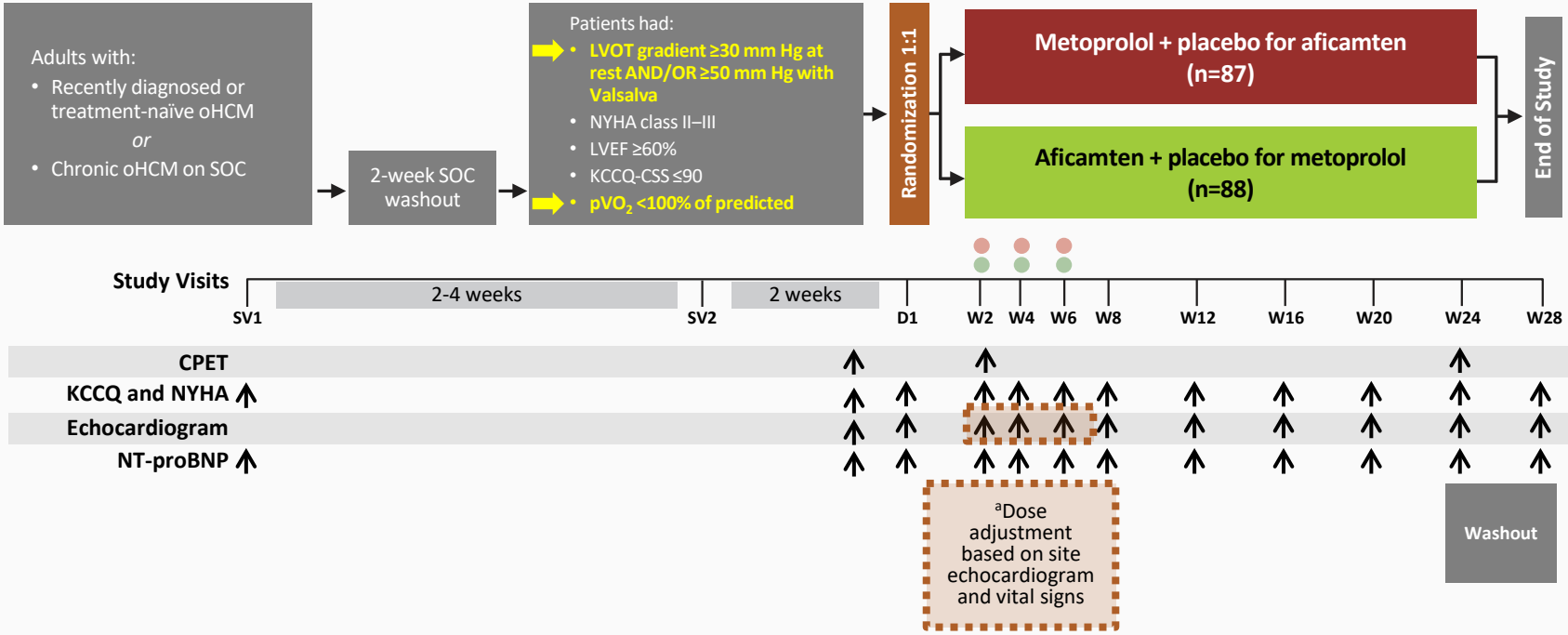
Background & Aims

- MAPLE-HCM[1] demonstrated that aficamten monotherapy was superior to metoprolol monotherapy in patients with symptomatic oHCM. Further, metoprolol failed to demonstrate any improvement in LVOT gradient
- Prior analyses of metoprolol dosing in MAPLE-HCM demonstrated that metoprolol was not effective at any dose level, whereas aficamten showed efficacy across all evaluated doses[2]
- Whether enrollment of predominantly beta-blocker resistant patients biased study results against detection of beta-blocker impact remains an outstanding question
- Evaluation of participants by pretrial treatment status (BB yes/no, SOC no) would be expected to reveal differences in beta-blocker treatment effect during the study because the BB-no group should be enriched with potential BB responders

The goal of this MAPLE-HCM substudy is to evaluate efficacy assessments by pretrial treatment status to elucidate any potential differential by BB-resistant enrollment

1. Garcia-Pavia P, et al. *N Engl J Med*. 2025;393(10):949-960. **2.** Masri A, et al. ESC-HF Presentation, May 11, 2026.
BB, beta blocker; LVOT, left ventricular outflow tract; oHCM, obstructive hypertrophic cardiomyopathy; SOC, standard of care.

MAPLE-HCM: Study Design



[a]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.

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

CPET, cardiopulmonary exercise testing; D, day; LVEF, left ventricular ejection fraction; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; 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; SOC, standard of care; SV, screening visit; W, week.

Methods

Participants randomized to **aficamten (5–20 mg daily)** or **metoprolol (50–200 mg daily)** for 24 weeks were grouped according to their pretrial medical therapy:

Groups 1 and 3 overlapped, as all SOC-no participants were also included in the BB-no group

BB, beta-blocker; SOC, standard of care.

Methods

Efficacy endpoints examined according to pretrial medical therapy:

- **Primary endpoint:**
  - Exercise capacity (change in pVO_2 from baseline to Week 24)

- **Key secondary endpoints:**
  - Symptoms: KCCQ-CSS, NYHA functional class
  - Hemodynamics: Valsalva LVOT gradient
  - Biomarkers: NT-proBNP

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake.

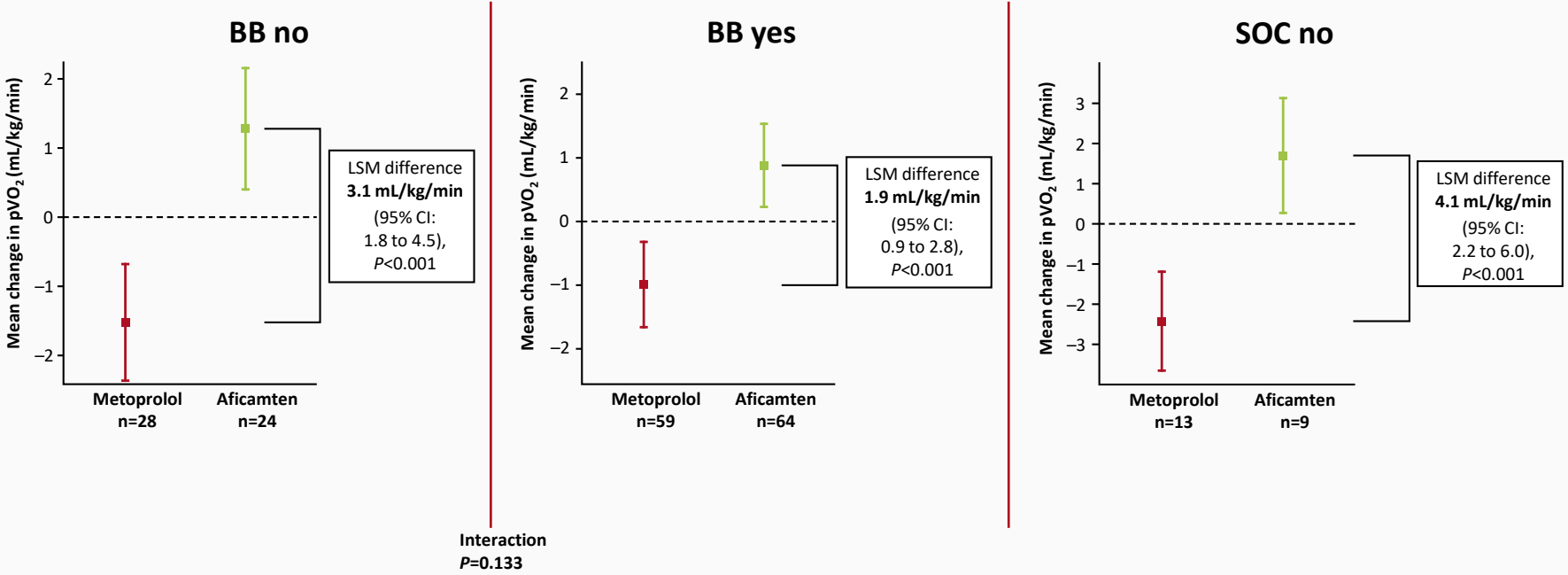
Results: Baseline Characteristics

	BB no	BB yes	SOC no
	N=52	N=123	N=22
Age, y	**55.7 ± 14.3**	**58.6 ± 12.7**	**55.0 ± 12.5**
Female	**17 (32.7)**	**56 (45.5)**	**7 (31.8)**
HCM-causing gene variant	9 (17.3)	19 (15.4)	3 (13.6)
Family history of HCM	11 (21.2)	23 (18.7)	4 (18.2)
Time since diagnosis, y	4.3 ± 4.1	5.8 ± 6.9	3.2 ± 4.0
Implantable cardioverter defibrillator	6 (11.8)	15 (12.3)	2 (9.1)
Septal myectomy	3 (5.9)	1 (0.8)	2 (9.1)
Hypertension	21 (40.4)	66 (53.7)	8 (36.4)
Diabetes	5 (9.6)	11 (8.9)	1 (4.5)
KCCQ overall summary score	59 ± 17	62 ± 17	66 ± 16
Symptoms			
NYHA class II	**34 (65.4)**	**89 (72.4)**	**18 (81.8)**
NYHA class III	**18 (34.6)**	**34 (27.6)**	**4 (18.2)**
Echocardiography			
LVEF at baseline, %	66 ± 4	68 ± 3	66 ± 5
LVOT at rest, mm Hg	42 ± 28	50 ± 29	48 ± 32
LVOT Valsalva, mm Hg	65 ± 33	77 ± 32	66 ± 36
pVO_2 at baseline CPET, mL/kg/min	21.0 ± 4.4	19.4 ± 5.2	21.4 ± 3.5
Biomarkers			
NT-proBNP at baseline, pg/mL	**458 [223, 893]**	**468 [195, 968]**	**326 [218, 655]**
High-sensitivity troponin I, ng/L	11 [7, 25]	14 [7, 29]	12 [8, 32]

Data are mean ± SD or n (%) unless otherwise indicated.
BB, beta-blocker; CPET, cardiopulmonary exercise testing; HCM, hypertrophic cardiomyopathy, 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; y, years.

Results: pVO_2 Change From Baseline to Week 24

Treatment with aficamten improved pVO_2 compared with metoprolol, **regardless of participants' pretrial medical therapy.**



BB, beta-blocker; CI, confidence interval; LSM: least squares mean; pVO_2, peak oxygen uptake; SOC, standard of care.

Results: Symptoms – KCCQ-CSS and NYHA Class

KCCQ-CSS and improvement of ≥1 NYHA functional class favored aficamten regardless of pretrial treatment.

Change in KCCQ-CSS at Week 24

	N	Aficamten[a]	N	Metoprolol[a]	Difference (95% CI)	*P*
BB no	24	15.1	27	8.4	7.6 (-0.3 to 15.6)	0.06
BB yes	63	16.0	59	8.9	6.5 (1.1–11.9)	0.019
SOC no	9	11.0	13	6.4	5.3 (-7.9 to 18.5)	0.782

[a]Values are mean change from baseline to Week 24.

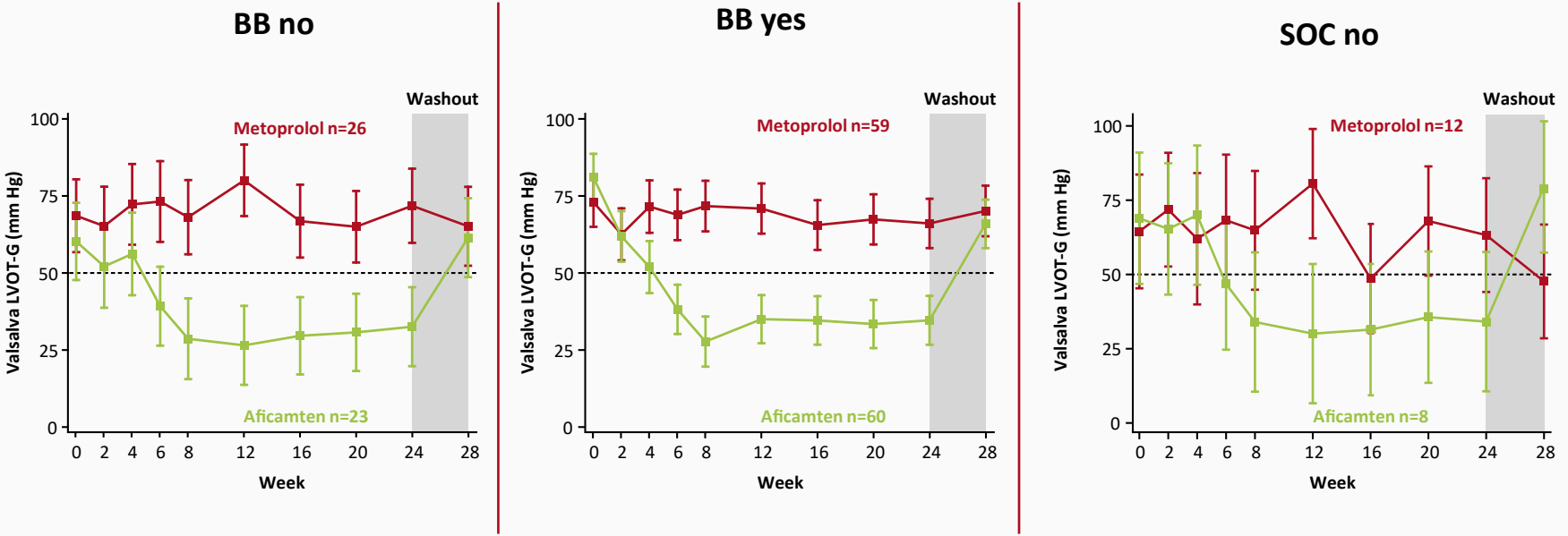
Improvement of ≥1 NYHA Functional Class at Week 24

	N	Aficamten[b]	N	Metoprolol[b]	Difference (95% CI)	*P*
BB no	24	42%	28	21%	19.1 (-7.8 to 46.1)	0.160
BB yes	64	55%	59	29%	26.7 (9.4–44.0)	0.003
SOC no	9	44%	13	15%	30.2 (-12.0 to 72.4)	0.151

[b]Difference between percentages of improvement of at least 1 NYHA functional class from baseline to Week 24.

BB, beta-blocker; CI, confidence interval; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NYHA, New York Heart Association; SOC, standard of care.

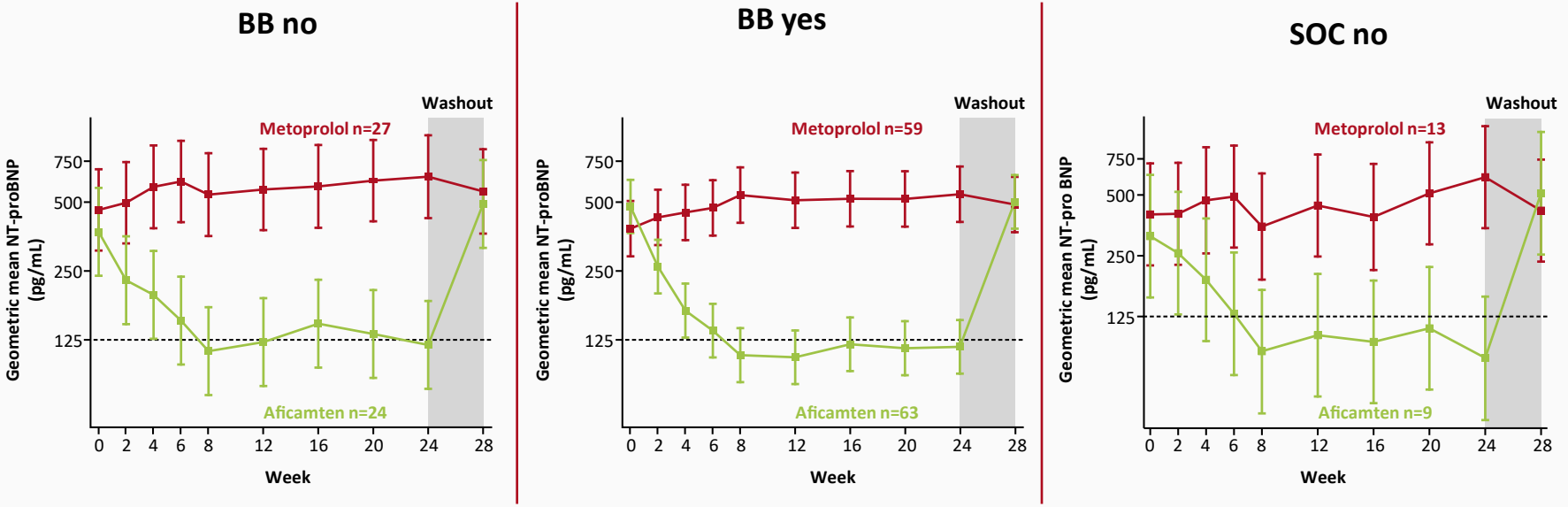
Results: Valsalva LVOT-G



Mean change in Valsalva LVOT-G mm Hg decreased significantly in aficamten vs metoprolol independent of pretrial treatment regimen: BB no: -26.6 vs 3.2, *P*<0.001; BB yes: -46.1 vs -6.9, *P*<0.001; SOC no: -32.8 vs -1.2, *P*= 0.068.

BB, beta-blocker; LVOT-G, left ventricular outflow tract gradient; SOC, standard of care.

Results: NT-proBNP



Geometric mean proportional change in NT-proBNP decreased significantly in aficamten vs metoprolol independent of pretrial treatment regimen:
BB no: -68% vs 45%, *P*<0.001; BB yes: -75% vs 41%, *P*<0.001; SOC no: -75 vs 53%, *P*<0.001.

BB, beta-blocker; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SOC, standard of care.

Safety

	Aficamten	Metoprolol
BB no, n (%)	**n=24**	**n=28**
Any SAE	2 (8.3)	3 (10.7)
Any TEAE	16 (66.7)	22 (78.6)
Any AE leading to early treatment withdrawal (including death)	0	2 (7.1)
Any AE leading to treatment interruption	0	0
LVEF <50%	0	0
BB yes, n (%)	**n=64**	**n=59**
Any SAE	5 (7.8)	3 (5.1)
Any TEAE	49 (76.6)	44 (74.6)
Any AE leading to early treatment withdrawal (including death)	1 (1.6)	1 (1.7)
Any AE leading to treatment interruption	1 (1.6)	1 (1.7)
LVEF <50%	1 (1.6)	0
SOC no, n (%)	**n=9**	**n=13**
Any SAE	0	1 (7.7)
Any TEAE	4 (44.4)	10 (76.9)
Any AE leading to early treatment withdrawal (including death)	0	0
Any AE leading to treatment interruption	0	0
LVEF <50%	0	0

AE, adverse event; BB, beta-blocker; LVEF, left ventricular ejection fraction; SAE, serious adverse events; SOC, standard of care; TEAE, treatment-emergent adverse event.

Conclusions

- The results of this MAPLE-HCM substudy support the primary study results regardless of pretrial treatment status: BB use at screening and prior SOC status
- These findings suggest that there is no confounding by selective enrollment of BB-resistant patients
- Aficamten can be considered as an early treatment option for patients with symptomatic oHCM, independent of prior SOC history

BB, beta-blocker; oHCM, obstructive hypertrophic cardiomyopathy; SOC, standard of care.

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ORIGINAL RESEARCH

Efficacy of Aficamten vs Metoprolol According to Pretrial Beta-Blocker Treatment in Obstructive Hypertrophic Cardiomyopathy

Insights From MAPLE-HCM

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ABSTRACT

BACKGROUND The MAPLE-HCM trial demonstrated the superiority of monotherapy with aficamten vs metoprolol at improving clinical endpoints in obstructive hypertrophic cardiomyopathy (oHCM). The impact of pretrial use of standard-of-care (SOC) medications, including beta-blockers (BBs), was unknown.

OBJECTIVES The aim of this study was to evaluate the efficacy of aficamten by pretrial medical therapy.

METHODS Participants were randomized to aficamten (5-20 mg/d) or metoprolol (50-200 mg/d) for 24 weeks. Exercise capacity and other efficacy endpoints were examined by pretrial medical therapy: 1) BB-no: participants not receiving any BB therapy at screening; 2) BB-yes: participants on BB at screening, regardless of duration of exposure; and 3) SOC-no: participants without SOC therapy for ≥12 months before screening. Groups 1 and 3 overlapped, as all SOC-no participants were also included in the BB-no group.

RESULTS A total of 175 patients were randomized. At screening, 52 participants were BB-no, 123 BB-yes, and 22 SOC-no. The overall mean age was 58 years; 41.7% of patients were women. The mean left ventricular outflow tract gradient was 47 mm Hg at rest and 74 mm Hg after the Valsalva maneuver. Aficamten demonstrated consistent benefits across multiple efficacy endpoints compared with metoprolol, independent of pretrial medical therapy. Aficamten improved exercise capacity (peak oxygen uptake) compared with metoprolol: BB-no: +3.1 mL/kg/min (95% CI: 1.8-4.5 mL/kg/min; $P < 0.001$); BB-yes: +1.9 mL/kg/min (95% CI: 0.9-2.8 mL/kg/min; $P < 0.001$) (P for interaction = 0.133); and SOC-no: +4.1 mL/kg/min (95% CI: 2.2-6.0 mL/kg/min; $P < 0.001$).

CONCLUSIONS Aficamten was superior to metoprolol regardless of BB use at screening or prior SOC medications. This supports the primary study results and suggests no confounding by BB resistance. Consequently, aficamten can be considered an early treatment option independent of prior SOC history. (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol Succinate in Adults With Symptomatic oHCM [MAPLE-HCM; NCT05767346)
(JACC Heart Fail. 2026;■:103352)

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