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Evaluation of Aficamten or Beta-Blocker Monotherapy Versus Placebo in Patients with Obstructive Hypertrophic Cardiomyopathy: A Pooled Analysis of SEQUOIA-HCM and MAPLE-HCM

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BACKGROUND

- Beta-blockers (BB) are first-line therapy for symptomatic obstructive HCM (oHCM) despite limited evidence.
- Aficamten reduces left ventricular outflow tract gradient (LVOT-G) and improves functional capacity and symptoms when added to background standard of care (SEQUOIA-HCM).[1]
- As monotherapy, aficamten is superior to metoprolol monotherapy (MAPLE-HCM).[2]
- To date, only limited data are available comparing the specific effects of aficamten or BB monotherapies with placebo.

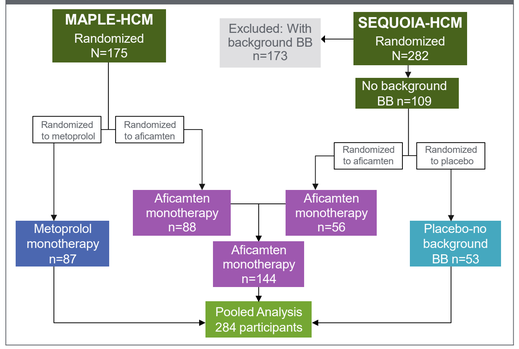
OBJECTIVE

- We leveraged 2 large prospective randomized controlled trials of aficamten in oHCM to compare the impacts of **aficamten, metoprolol, and placebo** in the treatment of symptomatic oHCM.

METHODS

- Participants from the SEQUOIA-HCM and MAPLE-HCM studies were pooled into 3 groups according to randomized treatment: aficamten, BB, or placebo (all monotherapy) (**Figure 1**).
- Changes in pVO_2, NYHA functional class, KCCQ-CSS, Valsalva LVOT-G, log-transformed NT-proBNP, and LVMI were compared across treatment groups after 24 weeks of follow-up.
- All analyses were adjusted for baseline cardiopulmonary exercise test modality (treadmill or cycle) and parent study.
- Analyses were adjusted for corresponding baseline values of each continuous outcome.

Figure 1. Flowchart of trial identification and selection for analysis



BB, beta-blocker.

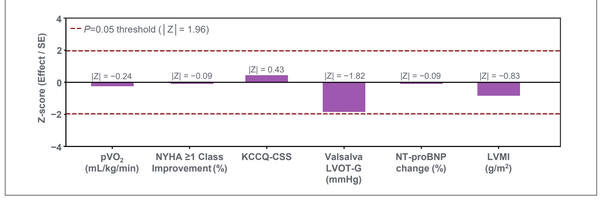
RESULTS

Table 1. Baseline demographics

	Aficamten n=144	Placebo n=53	Metoprolol n=87	*P* Value
Age, mean ± SD, years	60.0 ± 12.3	58.4 ± 13.3	56.5 ± 13.1	0.042
Sex (female), n (%)	63 (43.8)	25 (47.2)	37 (42.5)	0.90
Race, n (%)				0.55
Asian	27 (18.8)	16 (30.2)	12 (13.8)	
Other	7 (4.9)	0 (0.0)	5 (5.7)	
White	110 (76.4)	37 (69.8)	70 (80.5)	
Medical history, n (%)				
History of hypertension	87 (60.4)	28 (52.8)	33 (37.9)	<0.001
Known HCM-causing gene mutation	15 (10.4)	8 (15.1)	14 (16.1)	0.20
Positive family history of HCM	27 (18.8)	13 (24.5)	18 (20.7)	0.66
Paroxysmal atrial fibrillation	4 (2.8)	4 (7.5)	1 (1.1)	0.64
Coronary artery disease	18 (12.6)	8 (15.1)	12 (13.8)	0.76
Diabetes	10 (6.9)	2 (3.8)	10 (11.5)	0.27
Permanent atrial fibrillation	0 (0.0)	1 (1.9)	0 (0.0)	0.82
Vital signs, mean ± SD				
Systolic BP, mmHg	125 ± 15	125 ± 16	126 ± 14	0.51
Diastolic BP, mmHg	76 ± 10	75 ± 11	77 ± 9	0.36
Resting heart rate, bpm	79.0 ± 12.5	78.2 ± 13.2	80.5 ± 13.7	0.44
BMI at baseline, kg/m²	28.0 ± 3.6	27.1 ± 3.8	28.3 ± 3.6	0.68
Implantable cardioverter defibrillator, n (%)	9 (6.3)	4 (7.5)	13 (15.1)	0.030
KCCQ-CSS, mean ± SD	69 ± 18	74 ± 17	66 ± 16	0.29
NYHA class III/IV, n (%)	35 (24.3)	12 (22.6)	27 (31.0)	0.29
NT-proBNP, median [IQR], pg/mL	534 [256, 1048]	630 [274, 1096]	439 [171, 907]	0.20
hs-Troponin I, median [IQR], ng/L	14 [8, 37]	16 [9, 42]	12 [6, 25]	0.14

BMI, body mass index; BP, blood pressure; HCM, hypertrophic cardiomyopathy; hs, high-sensitivity; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy – Clinical Summary Score; Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

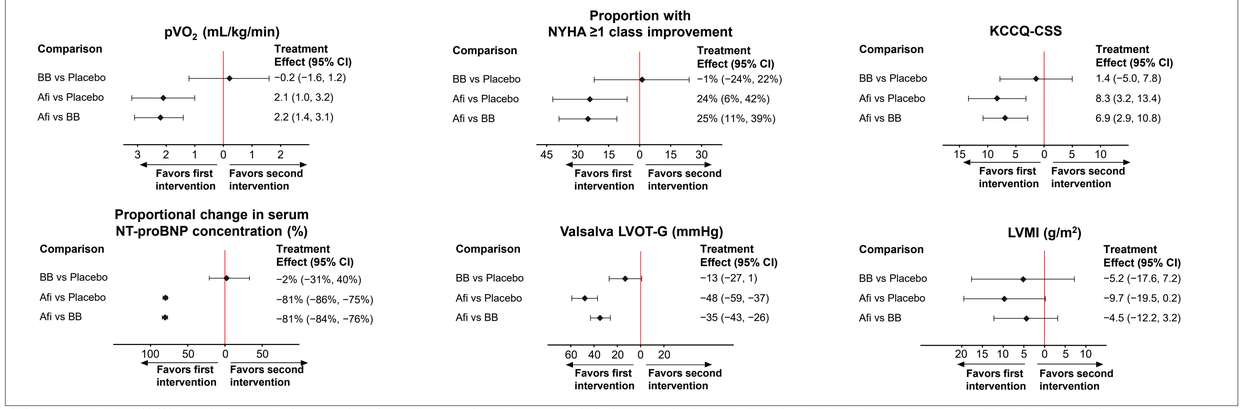
Figure 3. Metoprolol vs placebo: statistical significance of treatment effects across endpoints



Z-scores shown indicate statistical significance of estimated metoprolol vs placebo effects - treatment difference divided by its standard error. KSSQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVMI, left ventricular mass index; LVOT-G, left ventricular output tract gradient; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake; SE, standard error.

- There was no evidence of a treatment effect with BB compared with placebo in any of the efficacy endpoints.

Figure 2. Changes in efficacy from baseline to Week 24 in participants with oHCM



Afi, aficamten; BB, beta-blocker; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVMI, left ventricular mass index; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen uptake.

- Aficamten consistently improved efficacy relative to both placebo and metoprolol. Metoprolol was no different than placebo.

Table 2. Adverse events

n (%)	Aficamten n=144	Placebo n=53	Metoprolol n=87	*P* Value
Any serious AE	12 (8.3)	5 (9.4)	6 (6.9)	0.84
Any AE	109 (75.7)	39 (73.6)	66 (75.9)	0.95
Any AE leading to treatment discontinuation	1 (0.7)	1 (1.9)	3 (3.4)	0.27
Any AE leading to treatment interruption	2 (1.4)	0 (0.0)	1 (1.1)	1.00
Any core lab-reported LVEF <50% (Weeks 2–24)	4 (2.8)	1 (1.9)	0 (0.0)	0.33

AE, adverse event; LVEF, left ventricular ejection fraction.

- The proportion of participants with any serious AE or any AE was similar between each group.
- AEs leading to treatment discontinuation were more frequent in the metoprolol group.

CONCLUSIONS

- In participants with symptomatic oHCM, across many clinically relevant outcomes, including exercise capacity, symptoms, cardiac biomarkers, and gradients:
  - **BB monotherapy was *equivalent* to placebo.**
  - **Aficamten monotherapy was superior to both BB and placebo.**
- These findings support the emerging role of aficamten as first-line monotherapy in the treatment of symptomatic oHCM.

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SEQUOIA HCM | MAPLE HCM | Cytokinetics®

References

1. Maron MS, et al. *N Engl J Med* 2024;390(20):1849-61. doi:10.1056/NEJMoa2401424.
2. Garcia-Pavia P, et al. *N Engl J Med* 2025;393(10):949-60. doi:10.1056/NEJMoa2504654.

Disclosures

PCS: Honoraria and travel support: Bayer, AstraZeneca, Daiichi-Sankyo, Novartis, Actelion, Roche, Sanofi, Pharmacosmos, Medtronic, Thoratec, Boehringer Ingelheim, HeartWare, Coronus, Abbott, Edwards LifeSciences, Boston Scientific, St. Jude Medical, Abiomed, and the German Cardiac Society; research support: National Institutes of Health, the German Research Foundation, the Else Kröner Fresenius Foundation, the German Heart Foundation, the European Society of Cardiology, Actelion, Medtronic, the Federal Ministry of Education and Research of Germany, Abiomed, Boehringer Ingelheim, and Boston Scientific; advisory boards: German Research Council, Cytokinetics, Eurotransplant, Novartis, Bayer, Pharmacosmos, AstraZeneca, Boehringer Ingelheim, the German Cardiac Society, and the European Society of Cardiology.

Acknowledgments

The SEQUOIA-HCM and MAPLE-HCM trials were funded by Cytokinetics, Incorporated.
We thank the following individuals for their contributions to this clinical trial: Participants and their families, Investigators and study site staff, and Steering Committee members. Editorial support for the preparation of this presentation was provided by Engage Scientific Solutions, and was funded by Cytokinetics, Incorporated.