Efficacy and Safety of Aficamten in Patients with Obstructive Hypertrophic Cardiomyopathy and Mild Symptoms

Secondary analysis of aficamten efficacy and safety by symptom severity in patients in the SEQUOIA-HCM Trial

Iacopo Olivotto, MD, on behalf
of the SEQUOIA-HCM Investigators

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Background and objectives

- The subjectivity and heterogeneity of symptom burden in obstructive hypertrophic cardiomyopathy (oHCM) frequently results in undertreatment of patients with **objective measures of pathology** (such as impaired exercise capacity or elevated NT-proBNP) **and elevated gradients,** particularly **when symptoms are subtle**.
- However, even NYHA FC II symptoms may impact patients' lives considerably and have been associated with increased mortality in oHCM. These patients are not generally referred for invasive septal reduction therapies.[1]

Thus, patients with oHCM and mild symptoms, refractory to first-line medical therapy, present an unmet medical need

- SEQUOIA-HCM demonstrated treatment with aficamten substantially improved symptoms, functional capacity, and quality of life in patients with oHCM.[2]
- This secondary analysis was conducted to investigate the efficacy and safety of aficamten according to baseline symptom severity in patients in SEQUOIA-HCM.

NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA FC, New York Heart Association functional class.

1. Ahluwalia M, et al. *JACC Heart Fail* 2025;13(2):332-43. **2.** Maron MS, et al. *N Engl J Med* 2024;390(20):1849.

Methods

- Patients in SEQUOIA-HCM (N=282) were randomised 1:1 to aficamten or placebo once daily plus standard of care therapy for 24 weeks.[1]
- The dose of aficamten was titrated from 5 to 20 mg based on target LVOT-G and LVEF.[1]
- For this analysis, randomised patients were grouped according to baseline symptom severity. All comparisons were placebo-corrected.

Mild Symptoms (N=118 total; n=62 aficamten)
- NYHA FC II
- KCCQ-CSS ≥80

Moderate to Severe Symptoms (N=150 total; n=71 aficamten)
- NYHA FC II/III/IV
- KCCQ-CSS <80

Excluded from primary analysis (N=14 total)[a]
- NYHA FC III
- KCCQ-CSS ≥80

Primary Endpoint

Change in pVO_2 from baseline to Week 24

Secondary Endpoint

Changes from baseline to Week 24 in:

- NYHA FC
- NT-proBNP
- KCCQ-CSS
- Safety
- Resting and Valsalva LVOT-G

[a] To assess the impact of excluding these patients, a sensitivity analysis was performed by including them in both symptom groups; no differences in outcomes were observed.

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary score; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA FC, New York Heart Association functional class; pVO_2, peak oxygen uptake.

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

Baseline demographics and clinical characteristics

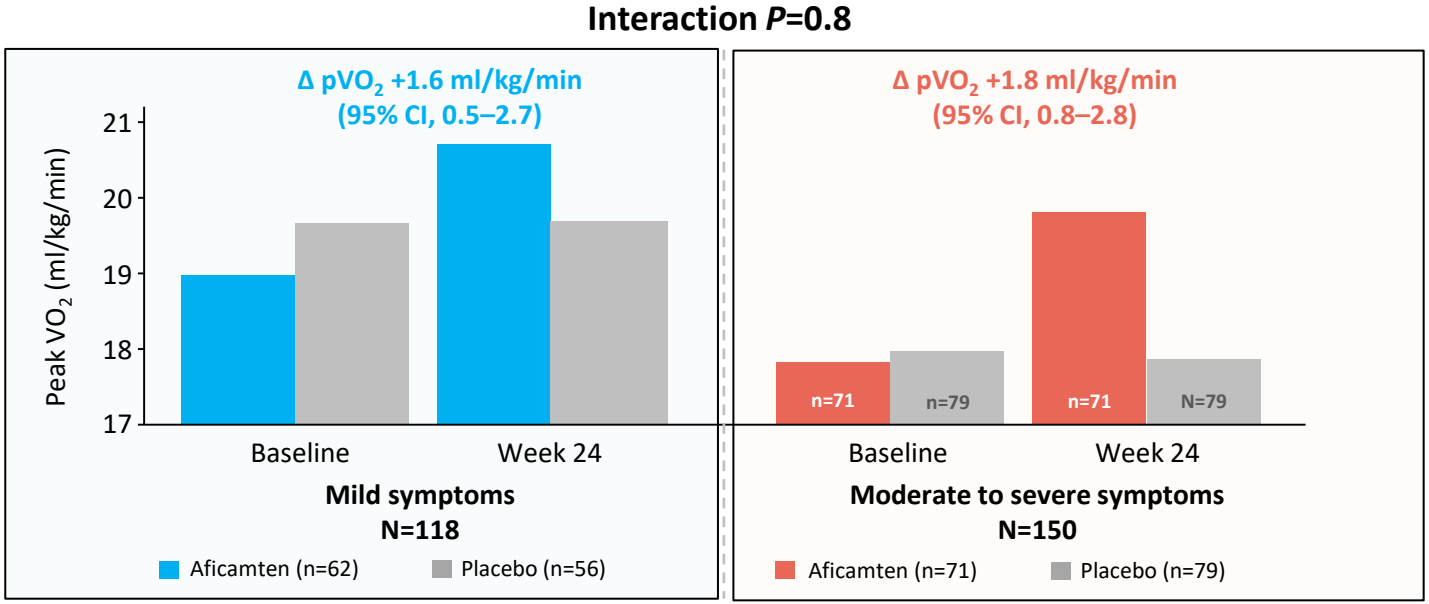
Characteristic, n (%), mean ± SD, or median [IQR]	Mild symptoms n=118	Moderate to severe symptoms n=150	*P* value
NYHA FC			<0.001
II	118 (100)	96 (64)	
III	0	53 (35)	
IV	0	1 (1)	
KCCQ-CSS	90 ± 6	61 ± 14	<0.001
Female sex	**36 (31)**	**71 (48)**	0.004
BMI, kg/m^2	**27 ± 4**	**29 ± 4**	0.003
Background beta-blocker	67 (57)	94 (63)	0.33
pVO_2 CPET, ml/kg/min	**19 ± 4**	**18 ± 4**	0.011
Valsalva LVOT-G, mmHg	81.4 ± 33.5	84.3 ± 31.4	0.46
LVEF, %	75.0 ± 6.0	74.7 ± 5.9	0.68
Max. LV wall thickness, cm	2.1 ± 0.3	2.1 ± 0.3	0.12
NT-proBNP, pg/ml	806 [317–1613]	676 [344–1737]	0.97
LAVI	39.7 ± 12.0	40.7 ± 15.3	0.58
LVMI	2.1 ± 0.3	2.1 ± 0.3	0.12

- Among all patients:
  - By design, KCCQ-CSS and NYHA FC were significantly different between groups.
  - Baseline characteristics of pVO_2, females, and BMI were also significantly different between the symptoms group.
  - All other baseline characteristics, including clinical and imaging variables, were similar between the symptoms group.

BMI, body mass index; CPET, cardiopulmonary exercise test; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary score; LAVI, left atrial volume index; LVMI, left ventricular mass index; max, maximum; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA FC, New York Heart Association functional class; pVO_2, peak oxygen uptake.

Primary endpoint: Functional improvement

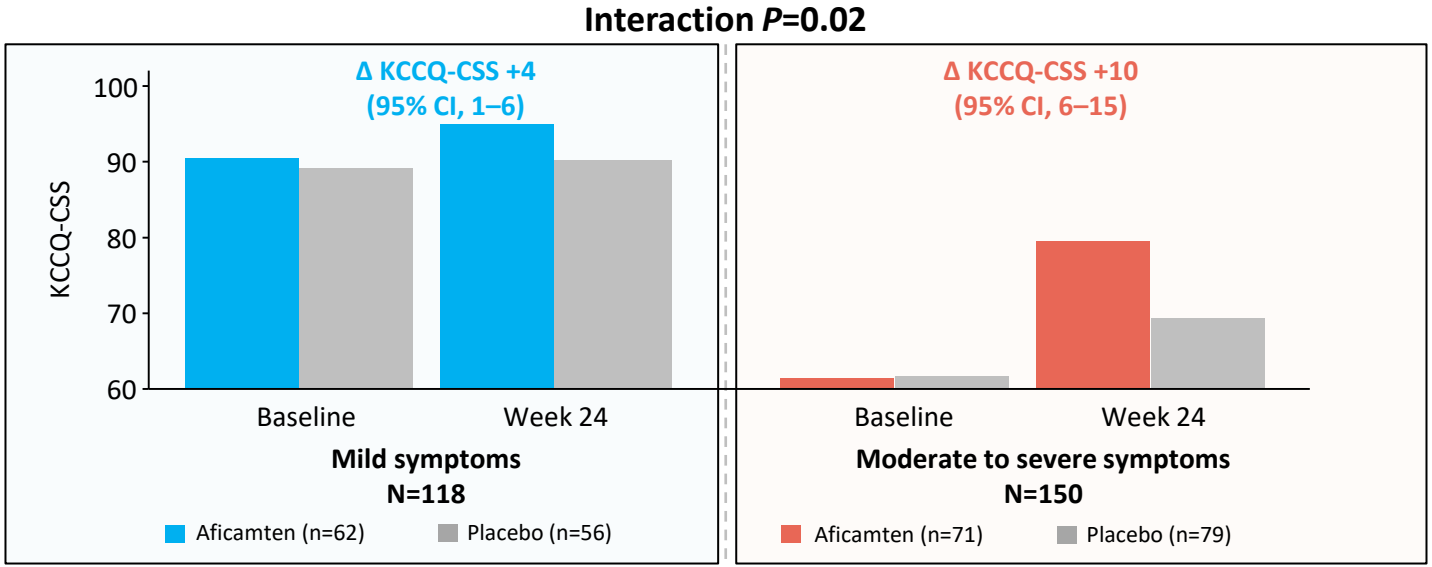
- Placebo-corrected **pVO_2 improved in both groups after aficamten treatment**.
- The treatment effect was **independent of the severity of symptoms**.



pVO_2, peak oxygen uptake.

Secondary endpoints: Health status by KCCQ-CSS

- Placebo-corrected **KCCQ-CSS improved in both groups after aficamten treatment**.
- As expected, the extent of improvement was significantly greater in those with more severe baseline symptoms, and prone to a ceiling-effect in those with high baseline KCCQ-CSS.

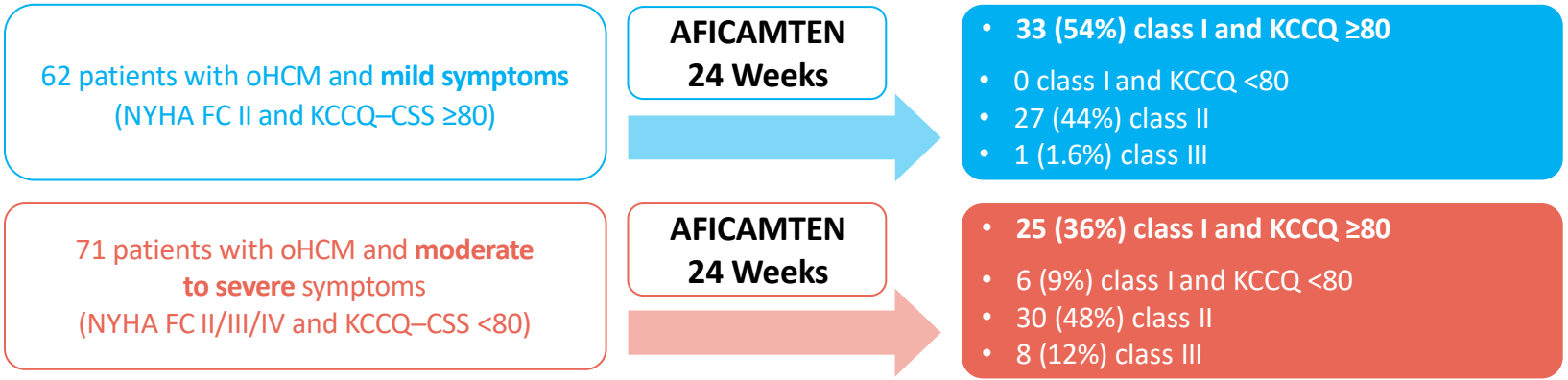


KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary score.

Secondary endpoints: Symptom burden by NYHA FC

Aficamten treatment groups only

- After 24 weeks of aficamten treatment, **53% (n=33/62) of patients with mild symptoms** and **58% (n=41/71) with moderate to severe symptoms** had an improvement of ≥1 NYHA FC (*P*=0.6).
- At Week 24, **more than half of patients with mild symptoms** and **more than one third with moderate to severe symptoms** became **asymptomatic** and reported good to excellent quality of life.



KCCQ-CSS categorises symptoms, function, and quality of life as very poor to poor (0–24), poor to fair (25–49), fair to good (50–74), or good to excellent (75–100).
KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary score; NYHA FC, New York Heart Association functional class; oHCM, obstructive hypertrophic cardiomyopathy.

Secondary endpoints: LVOT-G, cardiac structure, and biomarkers

Mean (95% CI) change from baseline to Week 24[a]	Mild symptoms n=62	Moderate to severe symptoms n=71	Interaction *P* value
Valsalva LVOT-G, mmHg	−53 (−62, −44)	−47 (−57, −37)	0.43
Resting LVOT-G, mmHg	−41 (−49, −33)	−38 (−47, −29)	0.64
Proportional change in NT-proBNP, %	−79 (−83, −73)	−81 (−85, −76)	0.56
LAVI, ml/m²	−4.6 (−7.3, −1.9)	−3.3 (−5.5, −1.2)	0.45
Max. LV wall thickness, cm	−0.16 (−0.25, −0.07)	−0.11 (−0.18, −0.03)	0.38

- LVOT-G, LAVI, maximum LV wall thickness, and NT-proBNP concentrations decreased in patients treated with aficamten (vs placebo), regardless of symptom severity.
- **74% (n=46/62) of patients with mild** and **62% (n=44/71) with moderate to severe symptoms** had a complete hemodynamic response (LVOT-G resting <30 mmHg and Valsalva <50 mmHg) with aficamten treatment.
- The effects of aficamten relative to placebo on outflow gradients, biomarkers, and measures of cardiac remodeling were similar between groups.

[a] Values presented are the placebo-corrected changes and were calculated from baseline to Week 24 using paired *t*-tests.
LAVI, left atrial volume index; LV, left ventricular; LVOT-G, left ventricular outflow tract gradient; max, maximum; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Secondary endpoints: Safety

Safety outcomes	Mild symptoms	Moderate to severe symptoms
	Aficamten vs placebo, n (%)	
Any treatment-emergent AE	49 (79) vs 35 (63)	51 (72) vs 61 (77)
Any treatment-emergent serious AE	0 (0) vs 5 (9)	8 (11) vs 8 (10)
LVEF <50%	3 (5) vs 0 (0)	2 (3) vs 1 (1)

- After 24 weeks of aficamten treatment:
  - Treatment-emergent serious AEs were infrequent in both symptom groups.
  - LVEF was similar between mild and moderate to severe symptom groups: least squares mean difference, +0.7% (95% CI, −1.8, +3.1).
  - There were no treatment interruptions or episodes of clinical heart failure/severe LV dysfunction in either group.

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

Conclusions

- **Patients with oHCM and mild symptoms treated with aficamten achieved significant improvement across a range of clinically relevant outcomes, including:**
  - Symptom relief
  - Exercise capacity
  - Early cardiac remodeling
  - NT-proBNP concentration
- For all clinical outcomes measured, the **magnitude of treatment benefit with aficamten in patients with mild symptoms was similar to that observed in patients with more advanced symptoms.**
- These data demonstrate the **clinical benefit of aficamten is independent of symptom burden** and support consideration of broader use of effective medical therapy to favourably impact natural history of disease progression in patients with oHCM.

NT-proBNP, N-terminal pro-brain natriuretic peptide; oHCM, obstructive hypertrophic cardiomyopathy.

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1 **Efficacy of Aficamten in Patients with Obstructive Hypertrophic Cardiomyopathy and**
2 **Mild Symptoms: Results from the SEQUOIA-HCM Trial**
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6 Martin S. Maron[a], Juan Ramon Gimeno [b], Josef Veselka[c], Roberto Barriales-Villa[d], Brian L.
7 Claggett[e], Caroline J. Coats[f], Sheila M. Hegde[g], James L. Januzzi[h,i], Ian J. Kulac[e], Ahmad
8 Masri[j], Michael E. Nassif[k], John A. Spertus[l], Daniel L. Jacoby[m], Stephen. B. Heitner[m], Stuart
9 Kupfer[m], Fady I Malik[m], Amy Wohltman[m], Iacopo Olivotto[n], on behalf of the SEQUOIA-HCM
10 Investigators
11
12 [a]Lahey Hospital and Medical Center, Burlington, MA, USA;
13 [b]Cardiac Department, University Hospital Virgen Arrixaca, CIBERCV, ERN Guard-Heart,
14 Murcia, Spain;
15 [c]Institute of Health Information and Statistics, Prague, Czech Republic;
16 [d]Complexo Hospitalario Universitario A Coruña, INIBIC, CIBERCV-ISCIII, A Coruña, Spain;
17 [e]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA,
18 USA;
19 [f]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, Scotland;
20 [g]Brigham and Women's Hospital, Boston, MA, USA;
21 [h]Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Harvard
22 Medical School, Boston, MA, USA;
23 [i]Baim Institute for Clinical Research, Boston, MA, USA;
24 [j]Oregon Health & Science University, Portland, OR, USA;

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