Aficamten is Safe and Effective in Obstructive Hypertrophic Cardiomyopathy With Comorbidities Obesity, Hypertension and Diabetes: A SEQUOIA-HCM Sub-study

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Background and Objectives

- Obesity, hypertension, and diabetes commonly coexist with obstructive hypertrophic cardiomyopathy (oHCM), potentially influencing symptom burden and functional limitation.[1-4]

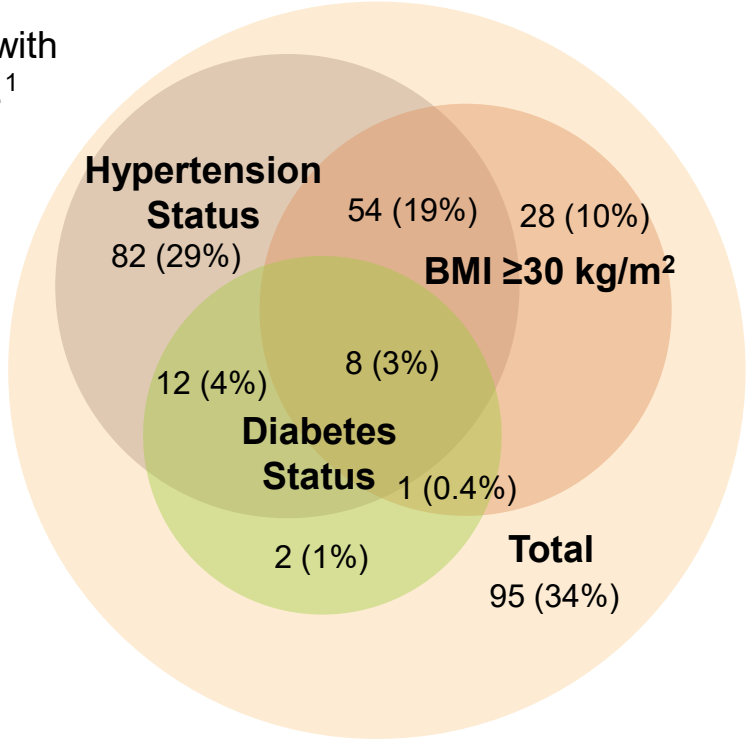
- Concerns about potential side effects and competing risks may deter initiation of cardiac myosin inhibitors (CMIs) in patients with multimorbidity.

- It is not known if aficamten provides similar benefit across comorbidity subgroups, or if the effect of treatment modifies these comorbidities.

1. Fumagalli, et al. *JAMA Cardiol* 2020;5:65.2. **2.** Lopes LR, et al. *Eur Heart J Qual Care Clin Outcomes* 2022;9:42-53.
3. Lu DY, et al. *Int J Cardiol Cardiovasc Risk Prev* 2023;16:200166. **4.** Smith JR, et al. *J Clin Med* 2018;7:447.

Methods

- SEQUOIA-HCM (NCT05186818) randomized 282 adults with symptomatic oHCM to aficamten or placebo for 24 weeks.[1]
- Participants were grouped by:
  - Obesity (BMI ≥30 kg/m^2)
  - Hypertension (history or average screening/baseline systolic blood pressure [SBP] ≥140 or diastolic blood pressure [DBP] ≥90 mmHg)
  - Diabetes (type 1, type 2, or unspecified per history)
- Baseline characteristics and treatment effects on peak oxygen uptake (pVO_2) and secondary endpoints were compared across comorbidity groups.



BMI, body mass index; oHCM, obstructive hypertrophic cardiomyopathy.

1. Maron MS, et al. *N Engl J Med* 2024;390:1849-61.

Results: Baseline Characteristics

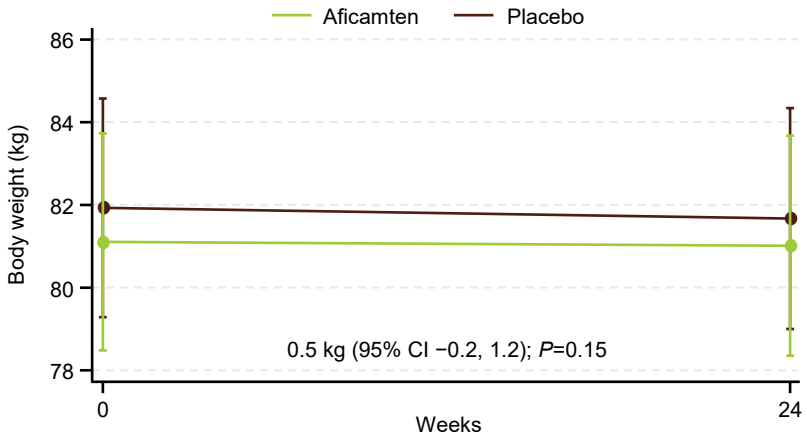
n (%); mean ± SD; median [IQR]	BMI <30 kg/m²	BMI ≥30 kg/m²	No Hypertension	Hypertension	No Diabetes	Diabetes
	n=191 (68%)	n=91 (32%)	n=126 (45%)	n=156 (55%)	n=259 (92%)	n=23 (8%)
Age	58.8 ± 13.5	59.7 ± 11.8	**54.5 ± 13.8**	**62.8 ± 10.9**	**58.6 ± 13.2**	**65.3 ± 7.7**
Female sex	80 (41.9)	35 (38.5)	47 (37.3)	68 (43.6)	105 (40.5)	10 (43.5)
Systolic blood pressure (mmHg)	124 ± 16	128 ± 15	**117 ± 13**	**131 ± 15**	125 ± 16	131 ± 19
Diastolic blood pressure (mmHg)	74 ± 11	75 ± 10	**72 ± 9**	**76 ± 11**	74 ± 10	73 ± 13
History of hypertension	**90 (47.1)**	**55 (60.4)**	0 (0.0)	145 (92.9)	**127 (49.0)**	**18 (78.3)**
History of AF (incl. paroxysmal)	24 (12.6)	19 (20.9)	**12 (9.5)**	**31 (19.9)**	39 (15.1)	4 (17.4)
History of diabetes	14 (7.3)	9 (9.9)	**3 (2.4)**	**20 (12.8)**	0 (0.0)	23 (100.0)
Age at HCM diagnosis (years)	52.6 ± 15.5	54.8 ± 12.2	47.8 ± 16.2	57.8 ± 11.2	52.7 ± 14.8	59.6 ± 9.1
ICD	25 (13.1)	14 (15.4)	21 (16.7)	18 (11.5)	36 (13.9)	3 (13.0)
KCCQ-CSS	**76.9 ± 16.8**	**70.0 ± 19.5**	76.0 ± 17.6	73.6 ± 18.3	74.3 ± 17.9	79.0 ± 19.0
NYHA Class III/IV	39 (20.4)	29 (31.9)	25 (19.8)	43 (27.6)	65 (25.1%)	3 (13.0)
NT-proBNP (ng/L)	**910 [434, 1982]**	**450 [278, 1118]**	**973 [494, 2199]**	**617 [282, 1380]**	797 [369, 1729]	528 [280, 1160]
Troponin I (ng/L)	13 [8, 38]	11 [8, 18]	13 [8, 32]	12 [7, 27]	12 [8, 27]	15 [8, 32]
eGFR (MDRD) (mL/min/1.73 m²)	89 [77, 105]	82 [65, 100]	92 [78, 109]	85 [69, 100]	87 [72, 103]	89 [65, 113]
pVO_2 (mL/kg/min)	**19.0 ± 4.4**	**17.4 ± 4.4**	**19.3 ± 4.6**	**17.9 ± 4.3**	18.6 ± 4.5	16.8 ± 4.1
Valsalva LVOT-G (mmHg)	85 ± 34	79 ± 28	85 ± 36	81 ± 29	83 ± 33	85 ± 24
Resting LVOT-G (mmHg)	**58 ± 31**	**50 ± 26**	**59 ± 32**	**52 ± 28**	55 ± 30	57 ± 24
Echo LV max wall thickness (cm)	2.08 ± 0.28	2.11 ± 0.33	2.12 ± 0.33	2.07 ± 0.27	2.09 ± 0.30	2.08 ± 0.29

AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LV, left ventricular; LVOT-G, left ventricular outflow tract gradient; MDRD, Modification of Diet in Renal Disease; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake.

Results by Obesity Status

Variable	BMI <30 kg/m²				
n (%) or mean (95% CI)	Aficamten n=97	Placebo n=94	Diff (95% CI)	*P* Value	$P_{interaction}$
pVO_2	1.8 (1.2, 2.5)	−0.0 (−0.7, 0.6)	1.8 (0.9, 2.7)	<0.001	0.77
KCCQ-CSS	11.2 (8.6, 13.8)	5.6 (3.2, 8.0)	6.6 (3.6, 9.6)	<0.001	0.37
Improved ≥1 NYHA	64 (66.0%)	24 (25.5%)	39.8 (26.9, 52.8)	<0.001	0.11
Valsalva LVOT-G	−49.4 (−57.6, −41.1)	−0.7 (−8.4, 7.0)	−50.4 (−59.0, −41.8)	<0.001	0.96
NT-proBNP[a]	0.18 (0.15, 0.21)	0.96 (0.86, 1.07)	0.19 (0.15, 0.22)	<0.001	0.33
n (%) or mean (95% CI)	BMI ≥30 kg/m²				
	Aficamten n=45	Placebo n=46	Diff (95% CI)	*P* Value	
pVO_2	1.7 (0.7, 2.7)	0.1 (−0.6, 0.8)	1.5 (0.4, 2.7)	0.011	
KCCQ-CSS	12.1 (7.8, 16.4)	3.0 (−0.7, 6.8)	9.0 (3.7, 14.4)	0.001	
Improved ≥1 NYHA	19 (42.2)	10 (21.7)	19.9 (0.7, 39.2)	0.043	
Valsalva LVOT-G	−43.9 (−53.2, −34.5)	7.1 (−2.3, 16.5)	−50.0 (−60.8, −39.3)	<0.001	
NT-proBNP[a]	0.24 (0.18, 0.32)	1.05 (0.91, 1.21)	0.22 (0.17, 0.30)	<0.001	

Body Weight from Baseline to Week 24



Safety	Aficamten		Placebo	
n (%)	BMI <30 kg/m² n=97	BMI ≥30 kg/m² n=45	BMI <30 kg/m² n=94	BMI ≥30 kg/m² n=46
Any SAE	5 (5.2)	3 (6.7)	10 (10.6)	3 (6.5)
Any LVEF <50%	3 (3.1)	2 (4.4)	0 (0.0)	1 (2.2)

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, New York Heart Association; pVO_2, peak oxygen uptake; SAE, serious adverse event.

[a] NT-proBNP geometric mean proportional change.

Results by Hypertension Status

Variable	No Hypertension				
n (%) or mean (95% CI)	Aficamten, n=61	Placebo, n=65	Diff (95% CI)	*P* Value	$P_{interaction}$
pVO_2	2.1 (1.3, 2.9)	0.1 (−0.7, 0.9)	2.0 (0.9, 3.1)	<0.001	0.46
KCCQ-CSS	13.5 (9.4, 17.6)	5.1 (2.4, 7.7)	8.1 (4.2, 12.0)	<0.001	0.57
Improved ≥1 NYHA	40 (65.6)	12 (18.5)	46.6 (31.3, 62.0)	<0.001	**0.042**
Valsalva LVOT-G	−50.2 (−61.2, −39.2)	−1.1 (−9.3, 7.1)	-49.5 (-59.6, -39.5)	<0.001	0.86
NT-proBNP[a]	0.18 (0.15, 0.23)	1.00 (0.88, 1.14)	0.20 (0.16, 0.25)	<0.001	0.96
n (%) or mean (95% CI)	Hypertension				
	Aficamten, n=81	Placebo, n=75	Diff (95% CI)	*P* Value	
pVO_2	1.5 (0.8, 2.2)	−0.1 (−0.7, 0.5)	1.4 (0.5, 2.3)	0.002	
KCCQ-CSS	10.0 (7.5, 12.4)	4.4 (1.4, 7.5)	6.3 (2.7, 9.9)	0.001	
Improved ≥1 NYHA	43 (53.1)	22 (29.3)	23.9 (8.5, 39.3)	0.003	
Valsalva LVOT-G	−45.7 (−53.3, −38.1)	4.3 (−4.5, 13.1)	−50.8 (−59.9, −41.6)	<0.001	
NT-proBNP[a]	0.20 (0.16, 0.25)	0.98 (0.87, 1.10)	0.20 (0.16, 0.25)	<0.001	

Safety	Aficamten		Placebo	
n (%)	No Hypertension, n=61	Hypertension, n=81	No Hypertension, n=65	Hypertension, n=75
Any SAE	1 (1.6)	7 (8.6)	4 (6.2)	9 (12.0)
Any LVEF <50%	3 (4.9)	2 (2.5)	0 (0.0)	1 (1.3)

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, New York Heart Association; pVO_2, peak oxygen uptake; SAE, serious adverse event.

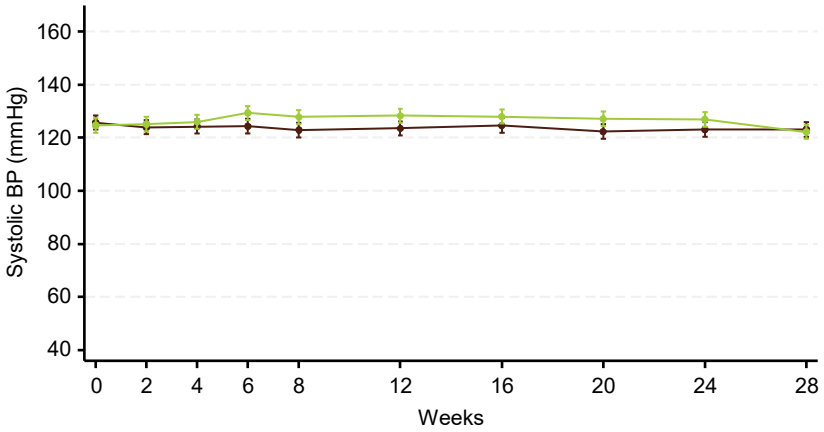
[a] NT-proBNP geometric mean proportional change.

Results By Hypertension Status

Systolic Blood Pressure from Baseline to Week 28

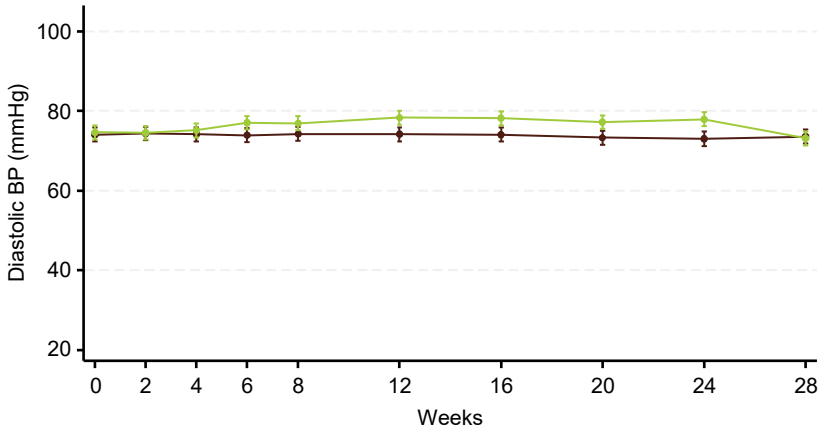
Aficamten — Placebo

+4.4 (95% CI 1.5, 7.3); ***P*=0.003**
W24 to W28: −3.4 (95% CI −6.5, −0.3); ***P*=0.03**



Diastolic Blood Pressure from Baseline to Week 28

+4.4 (95% CI 2.7, 6.2); ***P*<0.001**
W24 to W28: −3.9 (95% CI −5.8, −2.0); ***P*<0.001**



BP, blood pressure; W, week

Results: Hypertension

- Consistent with improved stroke volume from hemodynamic relief of aortic outflow obstruction, there was unmasking of underlying hypertension – a pattern also seen with prior CMI studies (including mavacamten), septal reduction therapy, and transcatheter aortic valve replacement.[1-6]

  – In the overall SEQUOIA-HCM population, systolic BP increases correlated, albeit weakly, with LVOT-G reductions (r = −0.12, 95% CI −0.24 to −0.00).

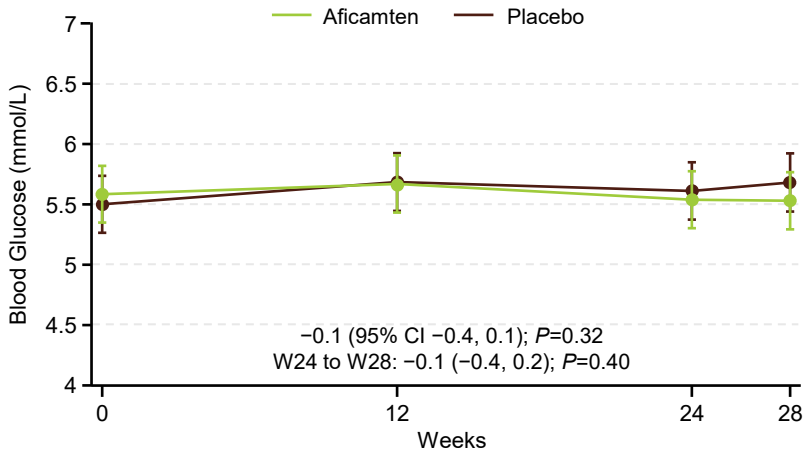
  – In non-obstructive HCM (REDWOOD-HCM Cohort 4; n=41) blood pressure response was flat (-0.5/-0.3 mmHg SBP/DBP) overall.

1. Reza N, et al. *J Am Coll Cardiol* 2024;83:564. **2.** Tian Z, et al. *JAMA Cardiol* 2023;8:957-65. **3.** Maurizi N, et al. *Eur Heart J Case Rep* 2024;8:ytae450.
4. Wang A, et al. *JACC Heart Fail* 2024;12:567-79. **5.** Timmer SAJ, et al. *Am J Physiol Heart Circ Physiol* 2011;301:H129-37.
6. Tiwari N, Madan NI. *Integr Blood Press Control* 2018;11:81-91.

Results: Diabetes Status

Variable	No Diabetes				
n (%) or mean (95% CI)	Aficamten n=128	Placebo n=131	Diff (95% CI)	*P* Value	$P_{interaction}$
pVO_2	1.8 (1.3, 2.4)	0.0 (−0.5, 0.5)	1.8 (1.0, 2.5)	<0.001	0.61
KCCQ-CSS	11.8 (9.4, 14.2)	4.7 (2.6, 6.8)	7.7 (4.9, 10.5)	<0.001	0.33
Improved ≥1 NYHA	73 (57.0)	31 (23.7)	33.5 (22.2, 44.8)	<0.001	0.86
Valsalva LVOT-G	−47.6 (−54.4, −40.8)	1.3 (−4.9, 7.5)	−49.6 (−56.6, −42.5)	<0.001	0.37
NT-proBNP[a]	0.19 (0.16, 0.22)	0.98 (0.90, 1.07)	0.19 (0.16, 0.22)	<0.001	0.40
	Diabetes				
n (%) or mean (95% CI)	Aficamten n=14	Placebo n=9	Diff (95% CI)	*P* Value	
pVO_2	1.2 (−0.0, 2.5)	-0.0 (−1.7, 1.7)	1.0 (−0.8, 2.7)	0.248	
KCCQ-CSS	8.5 (3.0, 14.1)	5.3 (-5.9, 16.6)	4.4 (−5.8, 14.5)	0.375	
Improved ≥1 NYHA	10 (71.4)	3 (33.3)	42.4 (−1.7, 86.4)	0.059	
Valsalva LVOT-G	−47.5 (−64.7, −30.2)	9.5 (−17.8, 36.7)	−62.0 (−86.6, −37.4)	<0.001	
NT-proBNP[a]	0.26 (0.18, 0.39)	1.04 (0.60, 1.81)	0.23 (0.13, 0.42)	<0.001	

Blood Glucose from Baseline to Week 28



Safety	Aficamten		Placebo	
n (%)	No Diabetes n=128	Diabetes n=14	No Diabetes n=131	Diabetes n=9
Any SAE	8 (6.3)	0 (0.0)	12 (9.2)	1 (11.1)
Any LVEF <50%	4 (3.1)	1 (7.1)	1 (0.8)	0 (0.0)

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, New York Heart Association; pVO_2, peak oxygen uptake; SAE, serious adverse event.

[a] NT-proBNP geometric mean proportional change.

Clinical Implications, Safety, and Limitations

- Small blood pressure increases with aficamten treatment are consistent with prior CMI data and adjacent literature on relief of aortic outflow obstruction.
- Although SEQUOIA-HCM excluded individuals with BMI ≥35 kg/m^2, no difference in efficacy or safety was observed across a wide range of body habitus.
- Although diabetes was classified categorically rather than using continuous metabolic measures (HbA1c), changes in blood glucose were not observed.
- Treatment duration was limited to 24 weeks with ongoing data being collected in FOREST-HCM (NCT04848506), the long-term open-label extension study.
- Despite broad inclusion criteria, the study population may not fully represent the complexity of real-world patients with oHCM and multimorbidity.

Conclusions

- The prevalence of comorbidities in the SEQUOIA-HCM population is broadly similar to that reported in large HCM cohorts (eg, SHARE, EORP Cardiomyopathy registry).[1,2]
- Aficamten treatment showed consistent clinical efficacy and safety in patients with and without obesity, hypertension, and diabetes.
- Aficamten is effective and well-tolerated even in multimorbid oHCM supporting its real-world utility.

1. Fumagalli, et al. *JAMA Cardiol* 2020;5:65.
2. Lopes LR, et al. *Eur Heart J Qual Care Clin Outcomes* 2022;9:42-53.