Aficamten in Patients with Obstructive Hypertrophic Cardiomyopathy: An Integrated Safety Analysis

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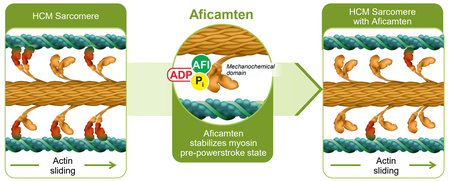
BACKGROUND

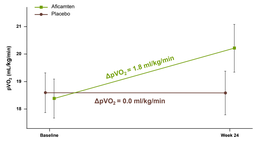
Aficamten is a next-in-class, oral, selective cardiac myosin inhibitor targeting the hypercontractility underlying HCM



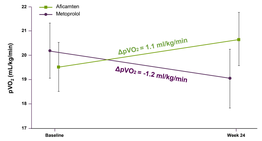
ADP, adenosine diphosphate; AFI, aficamten; HCM, hypertrophic cardiomyopathy; P_i, inorganic phosphate

SEQUOIA-HCM (NCT05186818)	Aficamten, as compared with placebo, improved exercise capacity, LVOT gradients, symptoms, and quality of life, with a modest effect on LVEF
MAPLE-HCM (NCT05767346)	Aficamten, as compared to metoprolol, improved exercise capacity.

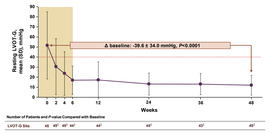
SEQUOIA-HCM
Absolute Change in pVO_2 from Baseline to Week 24



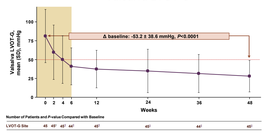
MAPLE-HCM
Absolute Change in pVO_2 from Baseline to Week 24



FOREST-HCM
Resting LVOT-G*



FOREST-HCM
Valsalva LVOT-G*



*Data cutoff of October 31, 2023. †P<0.001; ‡P<0.0001.
LVOT, left ventricular outflow tract; pVO_2, peak oxygen uptake.
Maron MS, et al. *N Engl J Med* 2024;390:1849-61. Saberi S, et al. *JACC Heart Fail*. Published online June 19, 2025.

PURPOSE AND METHODS

- To evaluate the integrated safety of aficamten across all recent and ongoing clinical trials
- All patients with oHCM who received ≥1 dose of aficamten or placebo/metoprolol in REDWOOD-HCM, SEQUOIA-HCM, MAPLE-HCM, or FOREST-HCM were included in this analysis as follows:
  - Placebo/metoprolol pool of REDWOOD-HCM, SEQUOIA-HCM, and MAPLE-HCM
  - Cumulative aficamten treated pool includes parent (REDWOOD-HCM, SEQUOIA-HCM, MAPLE-HCM) and extension (FOREST-HCM) studies

Trial	Phase	Design	Population	Duration	Status
REDWOOD-HCM Cohorts 1 & 2	2	Randomized placebo-controlled	oHCM (BB/CCB allowed) N=41	10 weeks on treatment	Completed
REDWOOD-HCM Cohort 3	2	Open label	oHCM + disopyramide (BB/CCB allowed) N=13	2 weeks washout	Completed
SEQUOIA-HCM	3	Randomized placebo-controlled	oHCM (BB/CCB/ Disopyramide allowed) N=282	24 weeks on treatment 4 weeks washout	Completed
MAPLE-HCM	3	Randomized comparison of aficamten to metoprolol	oHCM N=175	Pre-randomization SOC washout; 24 weeks on treatment 4 weeks washout	Completed
FOREST-HCM[a]	2–3	Open label extension; enrollment after completion of REDWOOD-HCM or SEQUOIA-HCM	oHCM + ability to withdraw BB/CCB/Disopyramide N=213	Up to 5 years	Ongoing

[a]Data cutoff: May 9, 2025. BB/CCB, beta-blocker/calcium channel blocker; oHCM, obstructive hypertrophic cardiomyopathy.

RESULTS

Baseline Characteristics

	Cumulative aficamten-treated pool[a]	REDWOOD-HCM			SEQUOIA-HCM		MAPLE-HCM		FOREST-HCM
	Aficamten	Cohorts 1-2 Placebo	Cohorts 1-2 Aficamten	Cohort 3 Aficamten	Aficamten	Placebo	Aficamten	Metoprolol	Aficamten
Number of participants	463	13	28	13	142	140	88	87	410
Mean age (years)	58.8	57.2	56.6	59.4	59.2	59.0	58.9	56.5	60.2
Sex, n (%)									
Female	195 (42.1)	8 (61.5)	15 (53.6)	7 (53.8)	56 (39.4)	59 (42.1)	36 (40.9)	37 (42.5)	179 (43.7)
Race, n (%)									
White	399 (86.2)	12 (92.3)	28 (100)	11 (84.6)	108 (76.1)	115 (82.1)	70 (79.5)	70 (80.5)	384 (93.7)
Non-white	64 (13.8)	1 (7.7)	–	2 (15.4)	34 (23.9)	25 (17.9)	18 (20.5)	17 (19.5)	26 (6.3)
Geographic region, n (%)									
North America	222 (47.9)	12 (92.3)	26 (92.9)	13 (100)	49 (34.5)	45 (32.1)	45 (51.1)	39 (44.8)	209 (51.0)
Europe/Rest of World	206 (44.5)	1 (7.7)	2 (7.1)	0	69 (48.6)	73 (52.1)	32 (36.4)	37 (42.5)	201 (49.0)
China	35 (7.6)	0	0	0	24 (16.9)	22 (15.7)	11 (12.5)	11 (12.6)	0
Background medical therapy									
BB	218 (47.1)	11 (84.6)	21 (75.0)	11 (84.6)	86 (60.6)	87 (62.1)	N/A	N/A	225 (54.9)
CCB (non-dihydropyridine)	121 (26.1)	4 (30.8)	10 (35.7)	3 (23.1)	51 (35.9)	46 (32.9)	N/A	N/A	105 (25.6)
Disopyramide	49 (10.6)	0	2 (7.1)	13 (100)	16 (11.3)	20 (14.3)	N/A	N/A	46 (11.2)
NYHA functional class									
I	5 (1.1)	0	0	0	0	0	0	0	14 (3.4)
II	319 (68.9)	11 (84.6)	17 (60.7)	5 (38.5)	108 (76.1)	106 (75.7)	63 (71.6)	60 (69.0)	244 (59.5)
III	139 (30.0)	2 (15.4)	11 (39.3)	8 (61.5)	34 (23.9)	33 (23.6)	25 (28.4)	27 (31.0)	152 (37.1)
IV	0	0	0	0	0	1 (0.7)	0	0	0

[a]Parent and extension studies, combined unique aficamten patients.
BB, beta blocker; CCB, calcium channel blocker; N/A, not applicable; NYHA, New York Heart Association.

697 Patient-Years of Exposure

	Cumulative aficamten-treated pool[a]	REDWOOD-HCM			SEQUOIA-HCM		MAPLE-HCM		FOREST-HCM
	Aficamten	Cohorts 1-2 Placebo	Cohorts 1-2 Aficamten	Cohort 3 Aficamten	Aficamten	Placebo	Aficamten	Metoprolol	Aficamten
Number of participants	463	13	28	13	142	140	88	87	410
Lost to follow-up, %	0	0	0	0	0	0	0	0	0
Study discontinuation, n(%)	11 (2.4)	0	0	0	3 (2.1)	3 (2.1)	1 (1.1)	1 (1.1)	7 (1.7)
Reason:									
Physician decision	2 (18.2)	0	0	0	0	2 (66.7)	0	0	2 (28.6)
AE	1 (9.1)	0	0	0	0	1 (33.3)	0	1 (100)	1 (14.3)
Withdrawal by participant	4 (36.4)	0	0	0	2 (66.7)	0	0	0	2 (28.6)
Death	2 (18.2)	0	0	0	0	0	1 (100)	0	1 (14.3)
Other	2 (18.2)	0	0	0	1 (33.3)	0	0	0	1 (14.3)
Mean duration of exposure, months	18.1	2.3	2.4	2.4	5.6	5.6	5.6	5.6	17.1
Total patient-years of exposure	696.5	3.5	7.6	3.5	76.5	75.5	41.0	40.5	582.2
Breakdown of maintenance daily dose[b,c], n (%)									
5 mg	27(6.5)	0	4 (14.3)	2 (15.4)	5 (3.6)	0	6 (6.8)	10 (11.5)	20 (6.3)
10 mg	77(18.5)	0	14 (50.0)	5 (38.5)	18 (12.9)	0	14 (15.9)	13 (14.9)	62 (19.6)
15 mg	143 (34.4)	0	5 (17.9)	6 (46.2)	49 (35.0)	0	34 (38.6)	17 (19.5)	105 (33.1)
20 mg	168 (40.4)	0	4 (14.3)	0	68 (48.6)	0	33 (37.5)	38 (43.7)	130 (41.0)
30 mg	1 (0.2)	0	1 (3.6)	0	–	–	–	–	–

[a]Parent and extension studies, combined unique aficamten patients. [b]N of patients included in the maintenance phase. [c]Metoprolol doses were 50, 100, 150, and 200 mg respectively. AE, adverse event.

Adverse Events

	Cumulative aficamten-treated pool[a]	Placebo/Metoprolol pool[b]		
	Aficamten N=463	Aficamten +/- SOC n=258	Placebo +/- SOC n=153	Metoprolol N=87
TEAE, n (%)				
Serious TEAE	65 (14.0), EAIR[c] 10.1	17 (6.6)	14 (9.2)	6 (6.9)
Leading to death	2 (0.4)	1 (0.4)	0	0
Leading to drug interruption	14 (3.0)	3 (1.2)	2 (1.3)	1 (1.1)
Leading to permanent discontinuation	4 (0.9)*	1 (0.4)	2 (1.3)	3 (3.4)
Common TEAE (≥5%)	**n (%)**	**EAIR[c]**		
COVID-19	63 (13.6)	10.0	16 (6.2)	10 (6.5)	4 (4.6)
Upper respiratory tract infection	51 (11.1)	7.6	21 (8.1)	12 (7.8)	10 (11.5)
Hypertension	49 (10.6)	7.4	20 (7.8)	4 (2.6)	3 (3.4)
Headache	48 (10.4)	7.5	21 (8.1)	14 (9.2)	6 (6.9)
Dizziness	43 (9.3)	6.5	17 (6.6)	3 (2.0)	15 (7.2)
Dyspnea	41 (8.9)	6.1	18 (7.0)	8 (5.2)	6 (6.9)
Palpitations	38 (8.2)	5.6	13 (5.0)	5 (3.3)	8 (9.2)
Nasopharyngitis	34 (7.3)	5.1	7 (2.7)	6 (3.9)	6 (6.9)
Atrial fibrillation	29 (6.3)	4.3	8 (3.1)	5 (3.3)	3 (3.4)
Back pain	28 (6.0)	4.0	7 (2.7)	2 (1.3)	2 (2.3)
Influenza	27 (5.8)	3.9	8 (3.1)	4 (2.6)	1 (1.1)
Fall	27 (5.8)	3.9	2 (0.8)	3 (2.0)	1 (1.1)
Urinary tract infection	26 (5.6)	3.8	6 (2.3)	1 (0.7)	0
Angina	25 (5.4)	3.6	12 (4.7	6 (3.9)	4 (4.6)
Arthralgia	25 (5.4)	3.7	1 (0.4)	2 (1.3)	2 (2.3)
Sinusitis	24 (5.2)	3.5	5 (1.9)	1 (0.7)	1 (1.1)

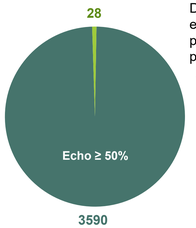
*Parent and extension studies, combined unique aficamten patients. [b]Placebo and study-initiated Metoprolol pool of REDWOOD-HCM, SEQUOIA-HCM, and MAPLE-HCM. [c]Incidence per 100 person-years
*Reasons: ischemic colitis, acute lymphocytic leukemia, humerus fracture, depression/suicide. SoC, standard of care; TEAE, treatment-emergent adverse event; EAIR, exposure-adjusted incidence rate

Safety Events of Interest

	Cumulative aficamten-treated pool[a]		Placebo/Metoprolol pool[b]		
	Aficamten N=463		Aficamten n=258	Placebo n=153	Metoprolol N=87
	n (%)	**EAIR[d]**			
LVEF <50%[c]	19 (4.1)	2.8	12 (4.7)	1 (0.7)	0
LVEF <50% with clinical heart failure*	3 (0.6)	0.6	1 (0.4)	1 (0.7)	0
Atrial fibrillation					
New onset	17 (3.7)	2.4	5 (1.9)	3 (2.0)	3 (3.4)
Recurrent	12 (2.6)	1.7	3 (1.2)	2 (1.3)	0
Heart Failure	13 (2.8)	1.9	5 (1.9)	2 (1.3)	1 (1.1)
Stroke	7 (1.5)	1.0	1 (0.4)	1 (0.7)	1 (1.1)
Myocardial infarction	15 (3.2)	2.2	6 (2.3)	5 (3.3)	4 (4.6)
Syncope	10 (2.2)	1.4	4 (1.6)	3 (2.0)	3 (3.4)
Death	2 (0.4)	0.1	1 (0.4)	0	0

*None of the 3 LVEF <50% associated with heart failure were corroborated by the Core Lab
[a]Parent and extension studies, combined unique aficamten patients. [b]Placebo/Metoprolol pool of REDWOOD-HCM, SEQUOIA-HCM, and MAPLE-HCM. [c]Site read. [d]Persons per 100 person years

Limited Echocardiogram Utility On Maintenance Aficamten



During the maintenance phases of the cumulative exposure pool, 3618 site-read echocardiograms were performed, with an average of 7.8 echocardiograms per patient

- 28 echocardiograms in 19 patients led to dose reductions due to site-read LVEF <50%
  - Only 2 were corroborated by the core laboratory
  - 5 discontinued or had treatment interruption (none had LVEF <40%)
  - 1 had an associated non-serious heart failure event
  - All had documented LVEF > 50% after dose adjustment, except for 1 patient who had history of LVEF < 50% on placebo in parent study

LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

CONCLUSIONS

In this integrated safety analysis of participants with oHCM with 697 patient-years of exposure, aficamten was well tolerated and had an adverse event profile similar to that of placebo

- There was a low incidence of LVEF <50%; no occurrences associated with clinical heart failure were corroborated by core lab, and all were successfully managed by dose reduction
- Low incidence of new-onset atrial fibrillation was comparable to placebo/metoprolol
- Incidence of syncope events were comparable to placebo/metoprolol despite much longer exposure to aficamten
- No permanent discontinuations related to aficamten
- Monitoring echocardiography in the maintenance phase yielded very few actionable results
- Overall, these results support the robust safety profile of aficamten and the uncomplicated management of patients with oHCM

FUTURE OUTLOOK

- Additional aficamten safety data is being generated in studies of patients with non-obstructive HCM (ACACIA-HCM), and with ongoing follow-up for both obstructive and non-obstructive HCM (FOREST-HCM)
- Ongoing CMR sub-studies in ACACIA-HCM and in FOREST-HCM will provide further insights on the ongoing remodeling in response to aficamten

Disclosures
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  - We thank the following individuals for their contributions to these clinical trials:
  - Participants and their families.
  - Investigators and study site staff.
  - Data Monitoring Committee members.
  - Steering Committee members.
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