Dosing and Safety Profile of Aficamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy

Results from SEQUOIA-HCM

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the SEQUOIA-HCM Investigators

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Disclosure

- Here are my disclosures

Background

- Aficamten is an investigational, novel, cardiac myosin inhibitor with unique physiochemical properties targeting the hypercontractility seen in patients with obstructive hypertrophic cardiomyopathy (oHCM)
- Exposure to cardiac myosin inhibitors have the potential for excessive reduction in contractile function and symptomatic heart failure (HF) [1, 2]
- Aficamten was engineered with the goal of achieving specific pharmacologic properties that allow for flexible dosing and increased safety [3]

Rapid onset

Rapid reversibility

Speed to optimal dose

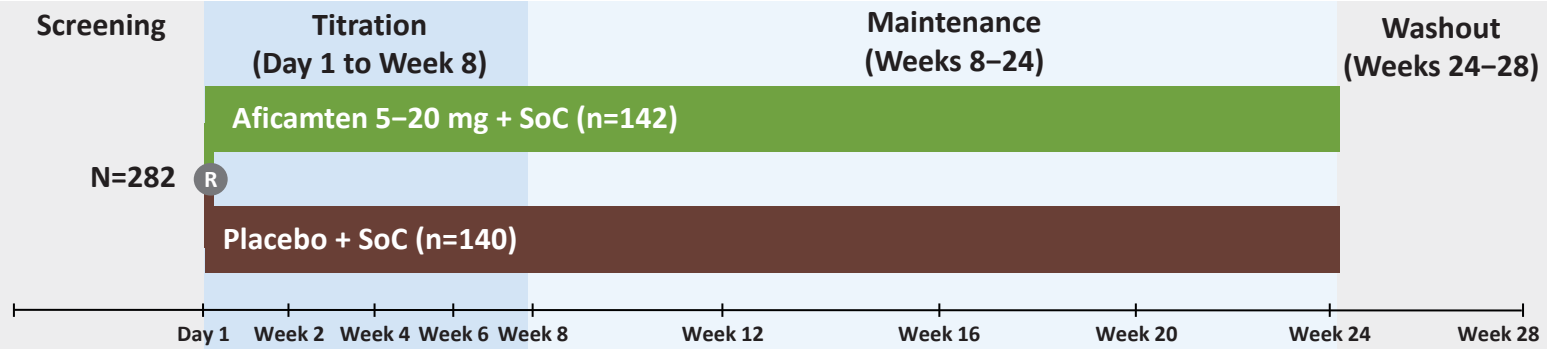
Predictable dose response

No teratogenicity

No clinically meaningful P450 liabilities

1. Olivotto I, et al. *Lancet* 2020;396(10253):758.
2. Heitner SB, et al. *Ann Intern Med* 2019;170(11):741-748.
3. Chuang C, et al. J Med Chem 2021:64(19):14142-14152.

Study Design

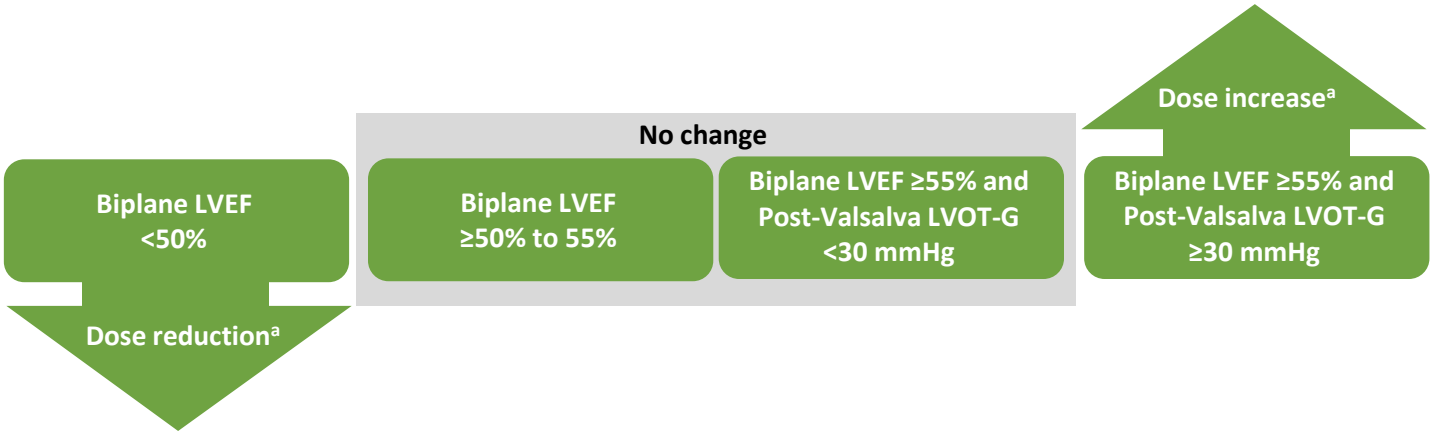


- Assessments were performed at screening and at each visit, and patients had 3 opportunities (Weeks 2, 4, and 6) for dose escalation
- SEQUOIA-HCM met its primary endpoint: improved peak oxygen uptake (pVO_2) at Week 24, measured by cardiopulmonary exercise testing
- This prespecified analysis by treatment phase (Titration, Maintenance, Washout):
  - Evaluated the safety of site-based echocardiographically-guided dose titration
    AND
  - Characterized the dose-concentration relationship and stability of plasma drug concentration during the maintenance phase

R, randomized (1:1) in a blinded manner; SoC, standard of care.

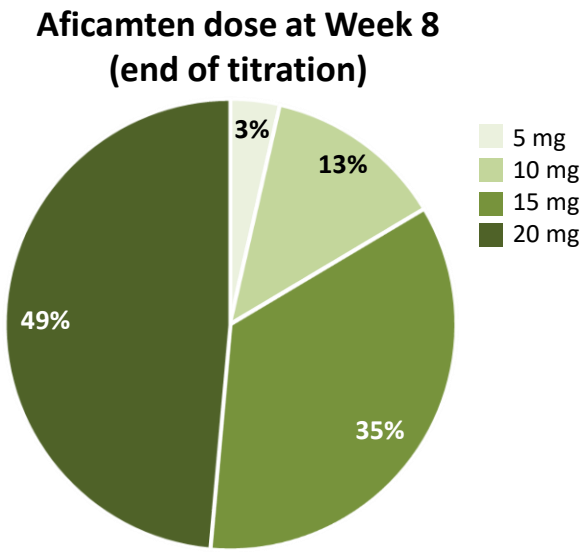
Dose Titration Scheme and Safety Outcomes

Site-based echocardiographically-guided dose titration algorithm



Individualised doses → Valsalva LVOT-G <30 mmHg and LVEF ≥50%

Baseline Characteristics by Aficamten Dose at Week 8 (end of titration)



- There were no differences in age, sex, ethnicity, body mass index, or comorbidities (diabetes, hypertension or AF) between dose groups

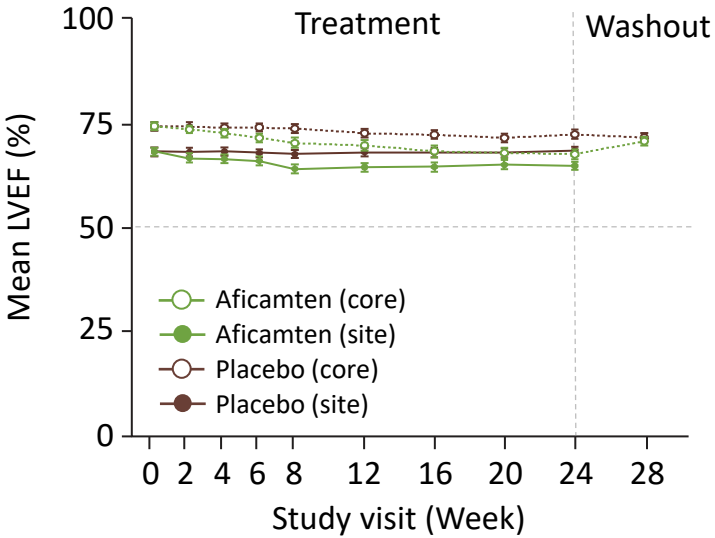
Mean ± SD, n (%), or median (IQR)	Placebo n=140	5 mg n=5	10 mg n=18	15 mg n=49	20 mg n=68
% per treatment group	100%	3.5%	12.7%	34.5%	47.9%
Background HCM therapy					
Beta-blocker	87 (62.1)	5 (100.0)	10 (55.6)	31 (63.3)	40 (58.8)
Calcium channel blocker	36 (25.7)	1 (20.0)	3 (16.7)	17 (34.7)	24 (35.3)
Disopyramide	20 (14.3)	1 (20.0)	5 (27.8)	3 (6.1)	7 (10.3)
Baseline study assessments					
KCCQ-CSS	74 ± 18	68 ± 26	75 ± 19	77 ± 20	75 ± 17
NYHA class II	106 (75.7)	3 (60.0)	16 (88.9)	33 (67.3)	54 (79.4)
NT-proBNP, pg/mL	692 (335, 1795)	1133 (992, 1475)	338 (283, 674)	871 (428, 1505)	962 (511, 2085)
hs-cTnI, ng/L	12 (8, 25)	12 (6, 234)	10 (5, 17)	13 (7, 24)	16 (8, 38)
pVO_2, mL/kg/min	18.6 ± 4.5	18.7 ± 2.9	18.6 ± 3.9	18.2 ± 4.1	18.3 ± 4.9
Echocardiographic parameters (core laboratory)					
LVEF at baseline, %	75 ± 6	71 ± 12	76 ± 5	75 ± 5	75 ± 5
Peak LVOT-G at rest	55 ± 32	29 ± 13	45 ± 21	56 ± 24	58 ± 30
Peak LVOT-G post-Valsalva	83 ± 33	51 ± 24	71 ± 29	84 ± 26	88 ± 35
Left ventricular MWT, cm	2.10 ± 0.30	2.42 ± 0.74	1.94 ± 0.22	2.04 ± 0.26	2.11 ± 0.28

hs-cTnI, high-sensitive cardiac troponin; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary score; MWT, maximal wall thickness; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association. Non-randomized groups

LVEF over the Study Period

Mean change in core laboratory LVEF over 24 weeks

Placebo corrected
ΔLVEF = -4.8%



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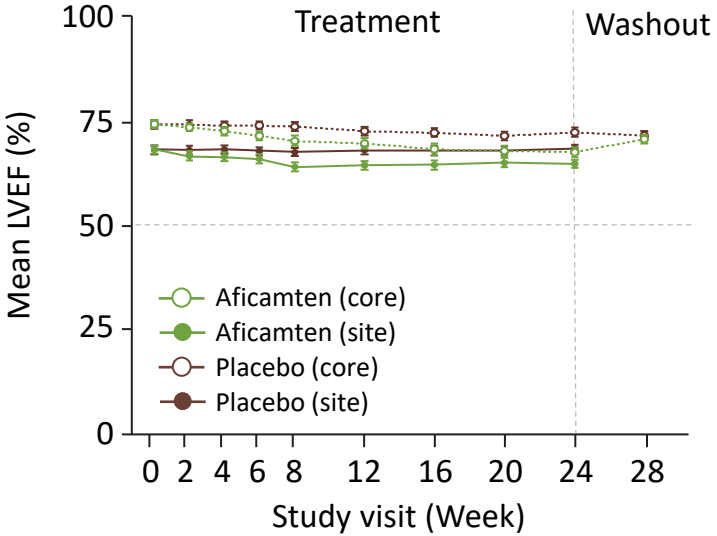
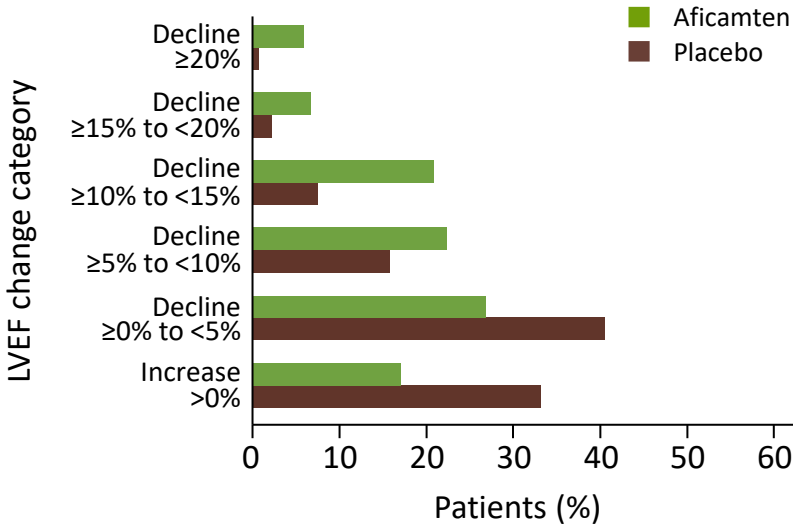
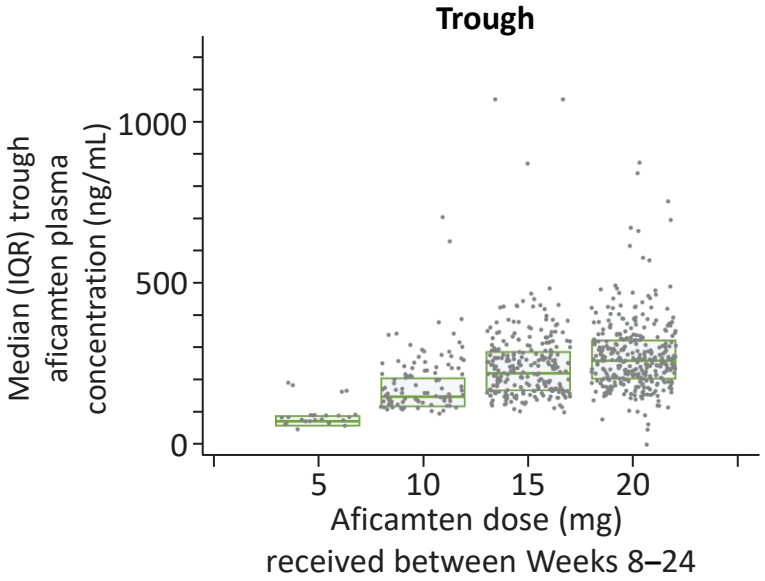


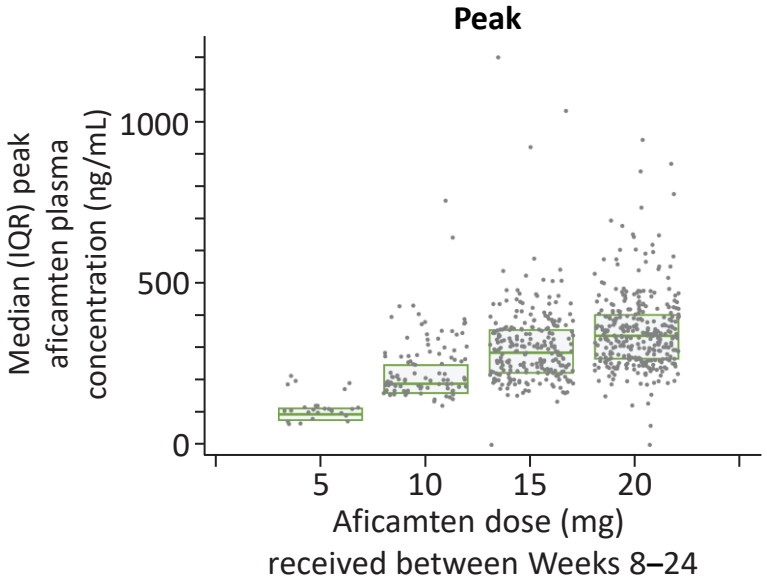
Distribution of categorical changes in core laboratory LVEF from baseline to Week 24



Plasma Drug Concentration: Maintenance Phase

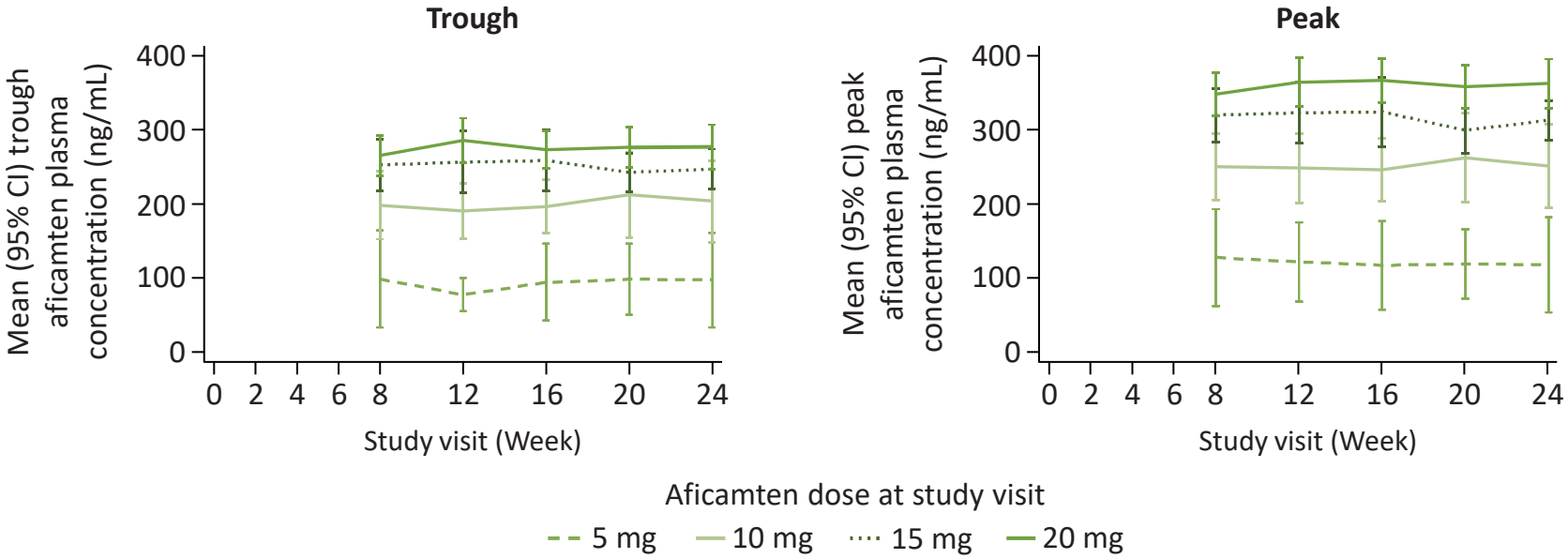
Trough and peak plasma drug concentrations for all available individual concentration measurements between Weeks 8–24 independent of study week





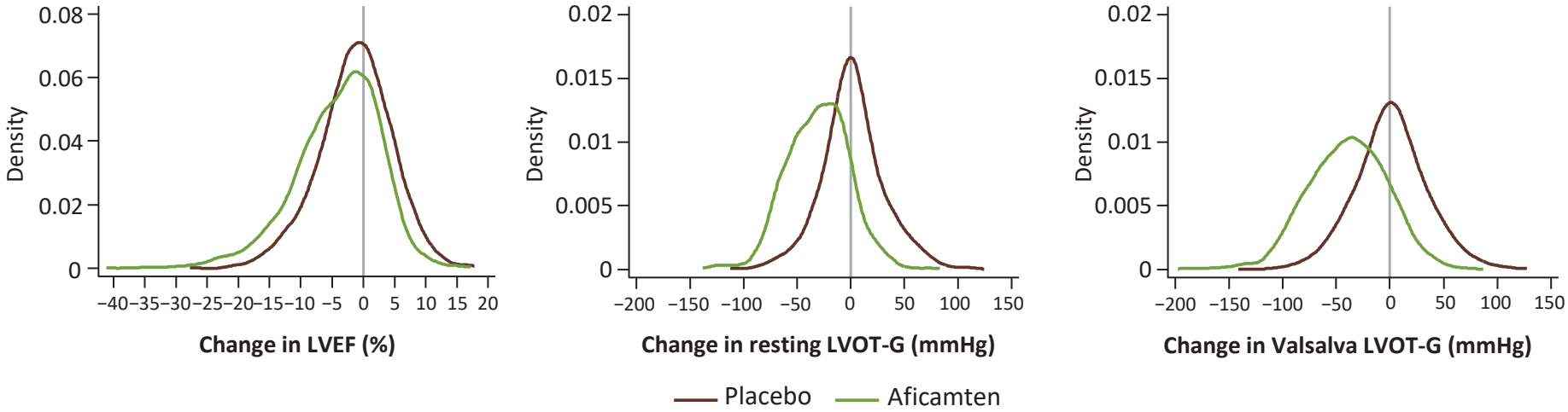
Plasma Drug Concentration: Maintenance Phase (continued)

Trough and peak plasma drug concentration by dose and study visit between Weeks 8–24



Distribution of Changes in Echocardiographic Parameters from Baseline at Each Study Visit

Small shifts from baseline in LVEF were associated with large reductions in LVOT-G



Gray vertical line denotes no change in echocardiographic parameter from baseline.

LVEF <50% (Site Read) Requiring Dose Adjustment

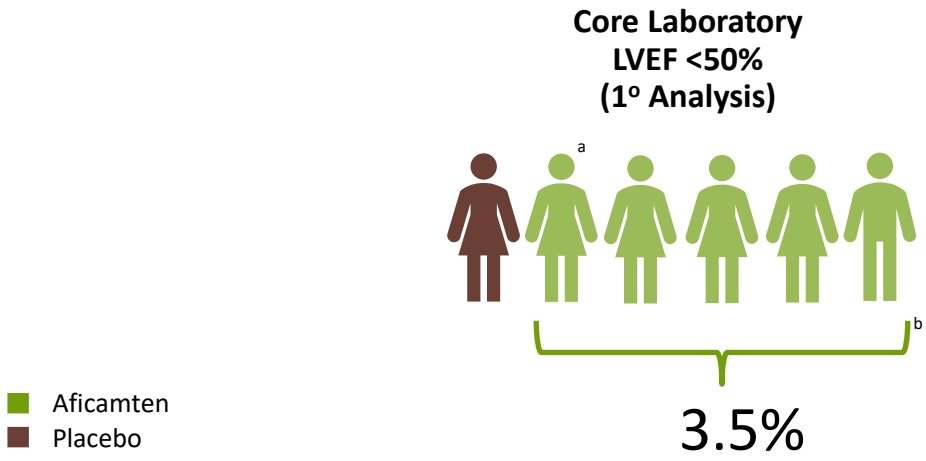
Site Interpreted LVEF <50%

- Aficamten
- Placebo

- No treatment interruptions occurred

[a] COVID-19 infection preceded LVEF <50% based on both core and site laboratory assessments.

Incidence of LVEF <50% (Core Laboratory)



- No treatment interruptions occurred
- No heart failure was experienced by any aficamten-treated patient with LVEF < 50% by either core laboratory or site interpreted
- All aficamten-treated patients with LVEF <50% were reversible

[a] COVID-19 infection preceded LVEF <50% based on both core and site laboratory assessments.
[b] Did not undergo dose adjustment

Safety Outcomes

AEs with ≥5% incidence

There were no serious adverse cardiovascular events associated with aficamten treatment in SEQUOIA-HCM

Event, n (%)	Placebo (n=140)	Aficamten (n=142)
Overall AEs	99 (70.7)	105 (73.9)
Headache	10 (7.1)	11 (7.7)
Hypertension	3 (2.1)	11 (7.7)
Palpitations	4 (2.9)	10 (7.0)
Upper respiratory infection	12 (8.6)	9 (6.3)
COVID-19	9 (6.4)	8 (5.6)
Dyspnea	8 (5.7)	8 (5.6)
SAEs	13 (9.3)	8 (5.6)
Cardiac AEs	21 (15.0)	24 (16.9)
Discontinuations	4 (2.9)	5 (3.5)
New-onset AF	1 (0.7)	1 (0.7)
Appropriate ICD shock	1 (0.7)	0
LVEF <50% by core laboratory[a]	1 (0.7)	5 (3.5)
Dose reduction based on site-read LVEF <50%	1 (0.7)	7 (4.9)

[a] 1 placebo- and 1 aficamten-treated patient overlap with dose reduction based on site-read LVEF <50%.

AE, adverse event; SAE, serious adverse event.

Conclusions

- Aficamten appeared safe and effective in the treatment of patients with oHCM in SEQUOIA-HCM using locally interpreted echocardiographic dose titration and monitoring
- There was a very low frequency of LVEF <50%, all asymptomatic
- There were no treatment interruptions for reduced LVEF
- The AE profile of aficamten was similar to that of placebo, with hypertension and palpitations occurring somewhat more frequently in the aficamten group

Acknowledgments

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