Effect of aficamten treatment on patients with hypertrophic obstructive cardiomyopathy by geographical region

Results from the SEQUOIA-HCM Trial

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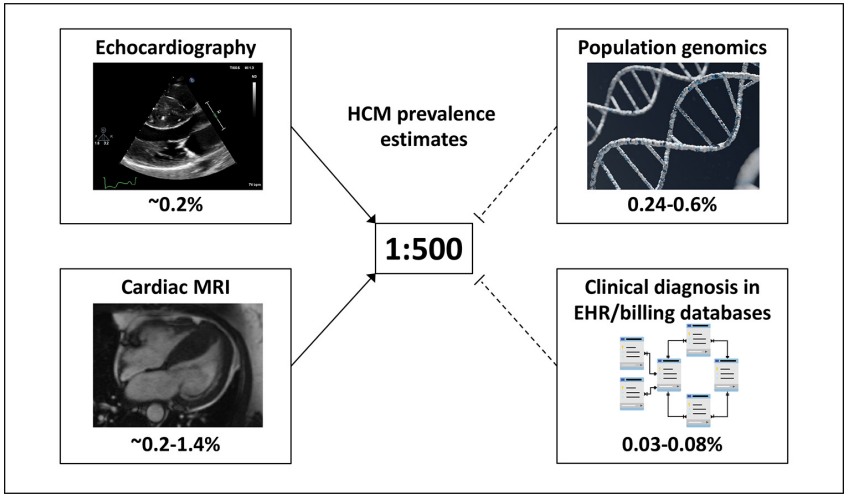
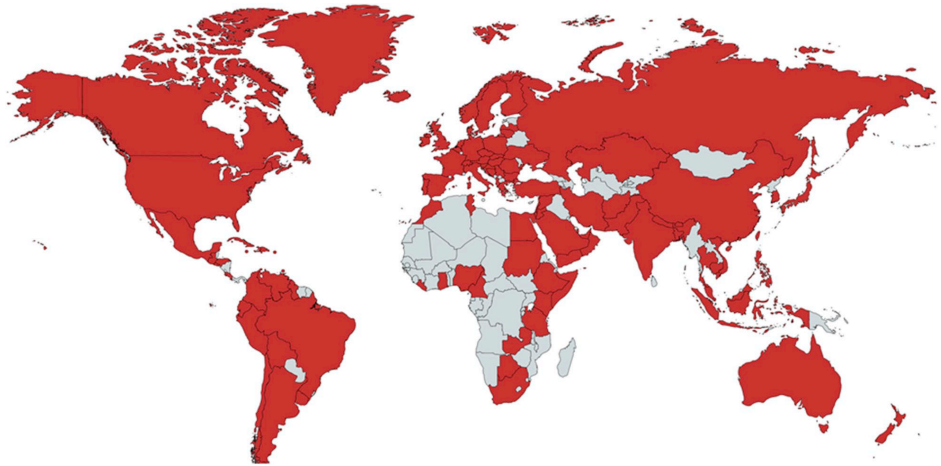
SEQUOIA HCM

Heart Failure & World Congress on Acute Heart Failure 2025

Global burden of hypertrophic cardiomyopathy

- HCM is a global disease.
- Access to contemporary treatments for obstructive HCM (myectomy, alcohol septal ablation and implantable cardioverter defibrillators) varies across the world.

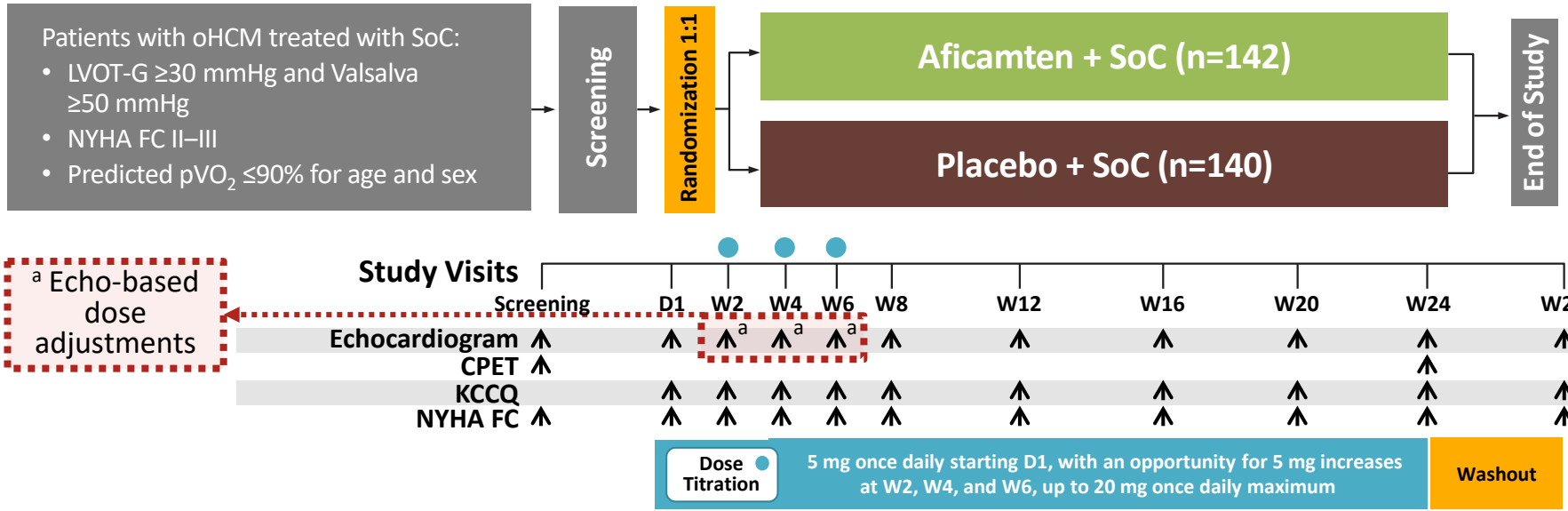




EHR, electronic health record; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; MRI, magnetic resonance imaging; oHCM, obstructive hypertrophic cardiomyopathy.

Maron MS, et al. *J Am Coll Cardiol HF* 2018;6(5):376; Massera D, et al. *Int J Cardiol* 2023;382:64.

SEQUOIA-HCM – Study design



Aficamten is a next-in-class cardiac myosin inhibitor with a half-life of ~3.4 days, a predictable and shallow dose-response relationship, and low liability for drug–drug interaction.

CPET, cardiopulmonary exercise testing; D, day; echo, echocardiogram; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT-G, left ventricular outflow tract gradient; NYHA FC, New York Heart Association functional class; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen uptake; SoC, standard of care; W, week.

Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215.

SEQUOIA-HCM: Geographic substudy objectives

Rationale: Geographic variation in patient characteristics and cardiovascular outcomes is well recognised in heart failure clinical trials.

Aim: To describe the impact of aficamten by geographic region in SEQUOIA-HCM.

Specific objectives were to:

1. Describe clinical characteristics of patients by geographic region.
2. Assess the treatment effects of aficamten by geographic region.
3. Assess the dosing and safety profile of aficamten by geographic region.

Regions included: USA (n=94 enrolled at 26 sites), China (n=46 enrolled at 12 sites), and Europe/Israel (n=142 enrolled at 44 sites).

Patient characteristics

Characteristic, n (%), mean ± SD	Europe and Israel n=142	China n=46	North America n=94	*P* value
Age, years	59.7 ± 12.5	51.8 ± 11.4	61.7 ± 13.2	<0.001
Female sex	54 (38.0)	16 (34.8)	45 (47.9)	0.21
BMI, kg/m²	28.3 ± 3.6	26.1 ± 3.3	28.7 ± 3.9	<0.001
Hypertension	67 (47.2)	17 (37.0)	61 (64.9)	0.003
Diabetes	14 (9.9)	0 (0.0)	9 (9.6)	0.09
Atrial fibrillation (including PAF)	23 (16.2)	1 (2.2)	19 (20.2)	0.019
Family history of HCM	48 (33.8)	8 (17.4)	19 (20.2)	0.021
Time since HCM diagnosis, years	7.1 ± 6.9	2.7 ± 3.2	5.3 ± 4.7	<0.001
ICD, %	22 (15.5)	0 (0.0)	17 (18.1)	0.010
Medication				
Beta-blocker	99 (69.7)	18 (39.1)	56 (59.6)	<0.001
Calcium channel blocker	37 (26.1)	23 (50.0)	37 (39.4)	0.006
Disopyramide	31 (21.8)	0 (0.0)	5 (5.3)	<0.001
No background therapy	15 (10.6)	12 (26.1)	9 (9.6)	0.012

Certain characteristics were more common in Europe and North America than in China, including:

- Older age
- Higher BMI
- Atrial fibrillation
- ICD use

BMI, body mass index; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; PAF, paroxysmal atrial fibrillation.

Baseline assessments

Characteristic, n (%), mean ± SD, or median [IQR]	Europe and Israel n=142	China n=46	North America n=94	*P* value
NYHA FC				<0.001
II	116 (81.7)	43 (93.5)	55 (58.5)	
III/IV	26 (18.3)	3 (6.5)	39 (41.5)	
pVO_2, ml/kg/min	18.8 ± 4.5	18.3 ± 4.7	18.2 ± 4.4	0.56
KCCQ-CSS	73.1 ± 18.6	82.4 ± 12.5	73.2 ± 18.6	0.006
NT-proBNP, median [IQR], ng/l	894 [410, 1869]	810 [317, 2252]	702 [284, 1212]	0.17
hs-cTnI, median [IQR], ng/l	13 [8, 27]	18 [6, 56]	10 [7, 20]	0.15
LV ejection fraction, %	75.2 ± 6.1	75.7 ± 4.8	73.7 ± 5.9	0.09
Resting LVOT-G, mmHg	53.3 ± 27.9	68.4 ± 33.0	51.2 ± 28.9	0.003
Valsalva LVOT- G, mmHg	83.7 ± 31.3	90.0 ± 35.8	78.7 ± 31.6	0.14
LV maximal wall thickness, cm	2.1 ± 0.3	2.2 ± 0.3	2.1 ± 0.3	0.06
LA volume index, ml/m^2	42.5 ± 14.9	40.5 ± 11.8	37.5 ± 12.8	0.028

Greater proportions of patients were NYHA class II in Europe and China than in North America.

Mean KCCQ-CSS and resting LVOT-G were higher among patients in China than in Europe or North America.

hs-cTnI, high-sensitivity cardiac troponin I; IQR, interquartile range; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LA, left atrial; LV, left ventricular; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro-hormone natriuretic peptide; NYHA FC, New York Heart Association functional class; pVO_2, peak oxygen uptake.

Treatment effects at Week 24

Change from baseline differences between aficamten and placebo by region

Endpoints	Europe and Israel n=142	China n=46	North America n=94	*P*-interaction
Primary endpoint:				
Change from baseline pVO_2 by CPET, ml/kg/min	+1.8	+1.8	+1.4	0.88
Secondary endpoints:				
KCCQ-CSS, change from baseline	+9.0	+3.5	+6.3	0.34
Proportion with NYHA ≥1 class improvement	+44.5%	+27.0%	+22.8%	0.18
Valsalva LVOT-G change from baseline, mmHg	–51.8	–59.8	–44.3	0.29
Proportion with Valsalva LVOT-G <30 mmHg	+51.7%	+51.0%	+34.8%	0.22
Change from baseline in total workload during CPET, watts	+7.5	+5.1	+5.5	0.98
Exploratory endpoint:				
Percentage change in NT-proBNP from baseline	–81%	–84%	–77%	0.34

Independent of geographic region, treatment with aficamten significantly improved exercise capacity, symptoms, outflow tract gradients, and cardiac biomarkers

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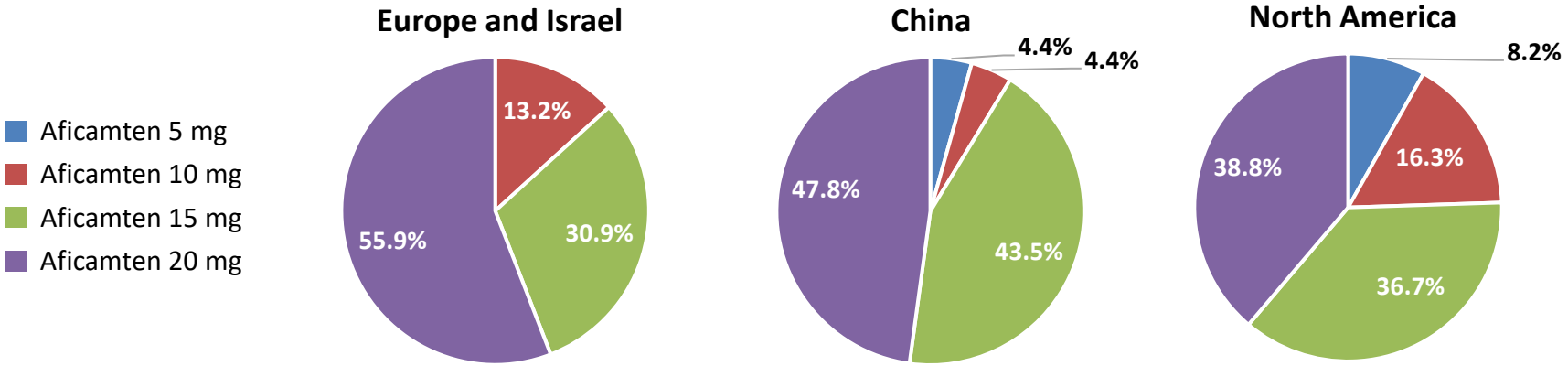
Differences are shown as the least squares mean difference between groups for the mean change from baseline for primary and secondary endpoints, except for proportions with NYHA ≥1 class improvement and Valsalva LVOT-G <30 mmHg, which are shown as risk differences representing treatment effects.
CPET, cardiopulmonary exercise testing; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro-hormone natriuretic peptide; NYHA, New York Heart Association; pVO_2, peak oxygen uptake.

Safety outcomes and dosing

Event, n (%)	Europe and Israel n=142	China n=46	North America n=94
Any serious AE			
Placebo	7 (9.6)	2 (9.1)	4 (8.9)
Aficamten	6 (8.7)	0 (0.0)	2 (4.1)
LVEF <50%			
Placebo	1 (1.4)	0 (0.0)	0 (0.0)
Aficamten	1 (1.4)	1 (4.2)	3 (6.1)

- The incidence of any serious AEs and occurrence of LVEF <50% were low and similar across regions.[a]
- Likewise, the distribution of doses achieved after titration was similar across regions.[b]



[a]Values for serious AEs and LVEF <50% are number (%) in each treatment arm.
[b]Percentages of patients at a given aficamten dose level were calculated using the total number of patients who received aficamten and had available dosing data (Europe and Israel: n=68; China: n=23; North America: n=49).
AE, adverse event during 24 weeks of treatment; LVEF, left ventricular ejection fraction.

Conclusions

- In SEQUOIA-HCM, aficamten treatment improved exercise capacity, symptoms, hemodynamics, and cardiac biomarkers independent of geographical region, despite differences in some baseline characteristics.

- Safety and dosing were similar across geographical regions.

- Clinical trials offer an opportunity to report a more global perspective of patient characteristics and how regional variation may contribute to therapeutic efficacy and safety.

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy.

SEQUOIA-HCM trial participants by geographic location

North America

USA:
94 enrolled, 26 sites

Older, higher BMI,
BB > CCB, ICDs,
lower KCCQ, NYHA FC III,
hypertension, diabetes, AF

China

China:
46 enrolled, 12 sites

Younger, lower BMI,
CCB > BB, no ICDs,
higher KCCQ; NYHA FC II,
coronary artery disease

Europe

Europe/Israel:
142 enrolled, 44 sites

Older, Higher BMI
BB > CCB, disopyramide, ICDs,
lower KCCQ, NYHA FC II,
hypertension, diabetes, AF

Similar peak VO_2, NT-proBNP, hs-cTnI, LVEF, and maximal wall thickness

Consistent dosing, safety and treatment effects of aficamten in obstructive hypertrophic cardiomyopathy

AF, atrial fibrillation; BB, beta-blocker; BMI, body mass index; CCB, calcium channel blocker; hs-cTnI, high-sensitivity cardiac troponin I; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-hormone natriuretic peptide; NYHA FC, New York Heart Association functional class; VO_2, oxygen uptake.

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