Effect of Aficamten on Patient-Reported Health Status in Obstructive Hypertrophic Cardiomyopathy: Results from SEQUOIA-HCM

Describing Patients' Perspectives of Treatment

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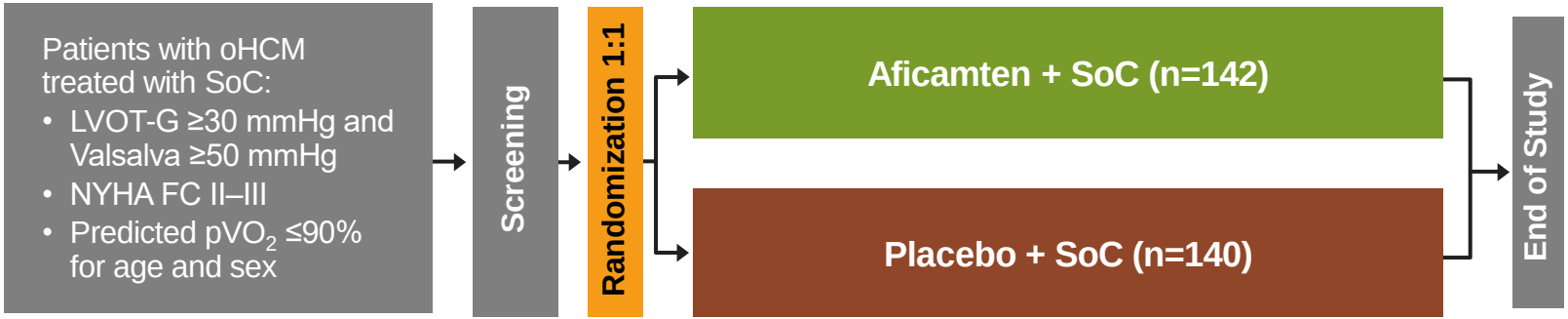
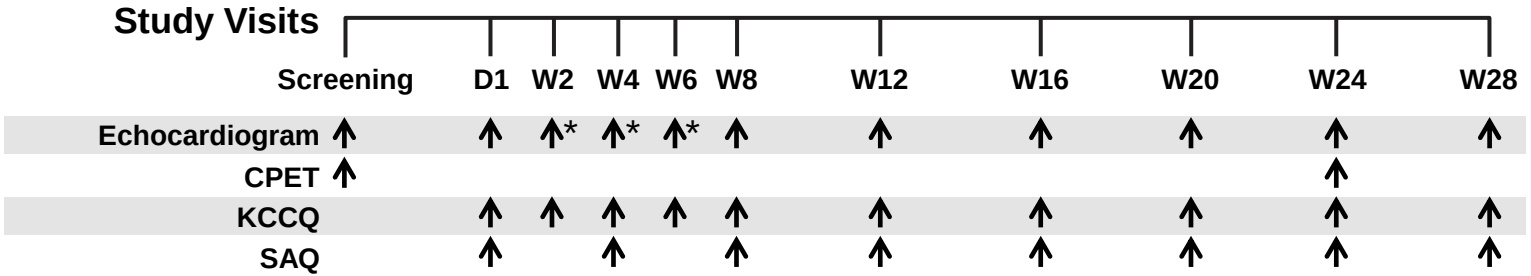
Background

- Left ventricular outflow tract (LVOT) obstruction in HCM can cause significant symptoms limiting patients' function and quality of life.
- Aficamten is a novel oral cardiac myosin inhibitor that reduces LVOT and improves exertional capacity.

HCM, hypertrophic cardiomyopathy.

SEQUOIA-HCM – Study Design





CPET, cardiopulmonary exercise test; D, day; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVOT-G, LVOT gradient; NYHA FC; New York Heart Association functional class; oHCM, obstructive HCM; pVO_2, peak oxygen consumption; SAQ, Seattle Angina Questionnaire; SoC, standard of care; W, week. *Dose adjustment based on site-read echocardiograms.

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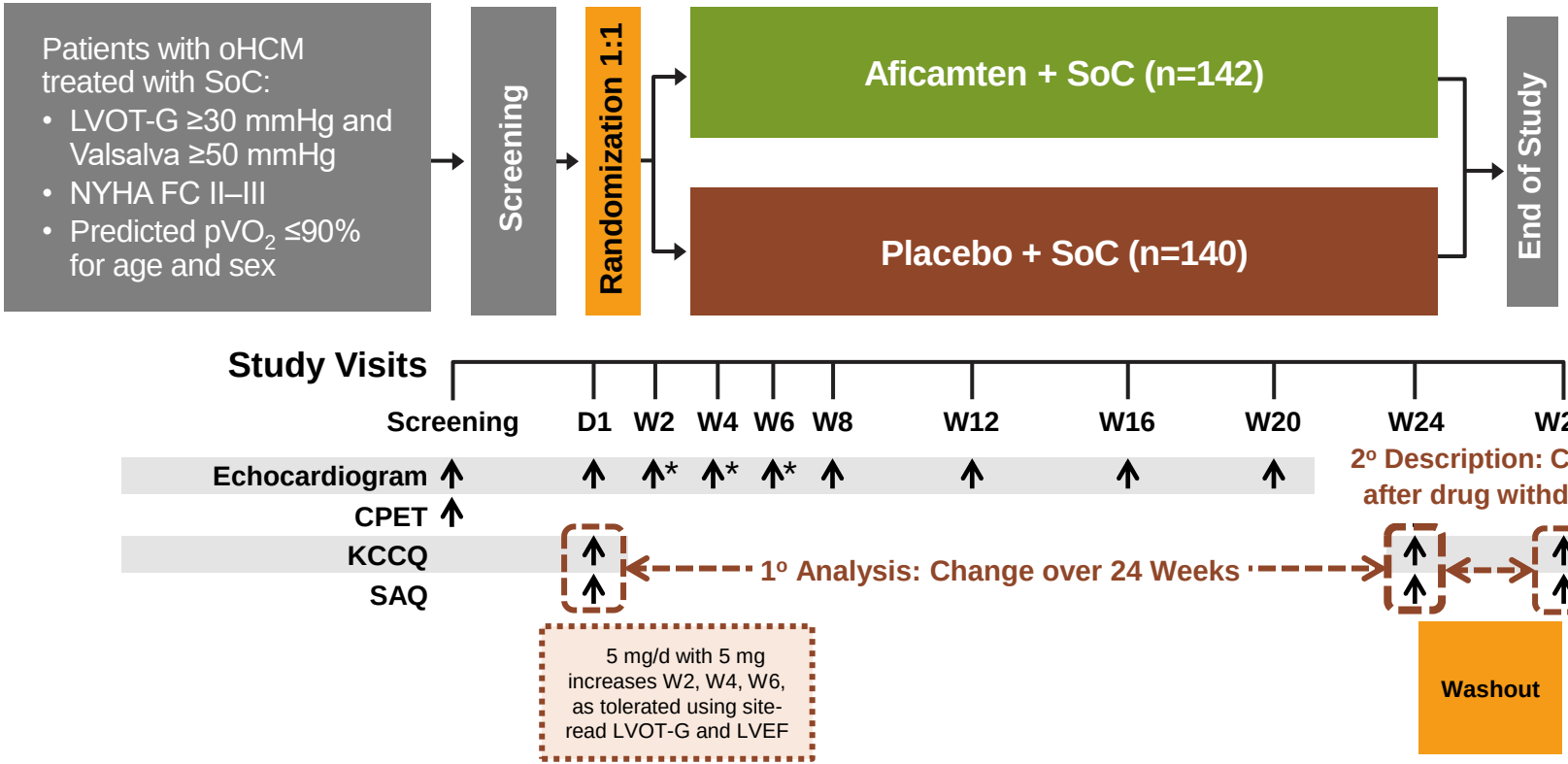


CPET, cardiopulmonary exercise test; D, day; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; LVOT-G, LVOT gradient; NYHA FC; New York Heart Association functional class; oHCM, obstructive HCM; pVO_2, peak oxygen consumption; SAQ, Seattle Angina Questionnaire; SoC, standard of care; W, week. *Dose adjustment based on site-read echocardiograms.

Measuring Patients' Health Status – The KCCQ

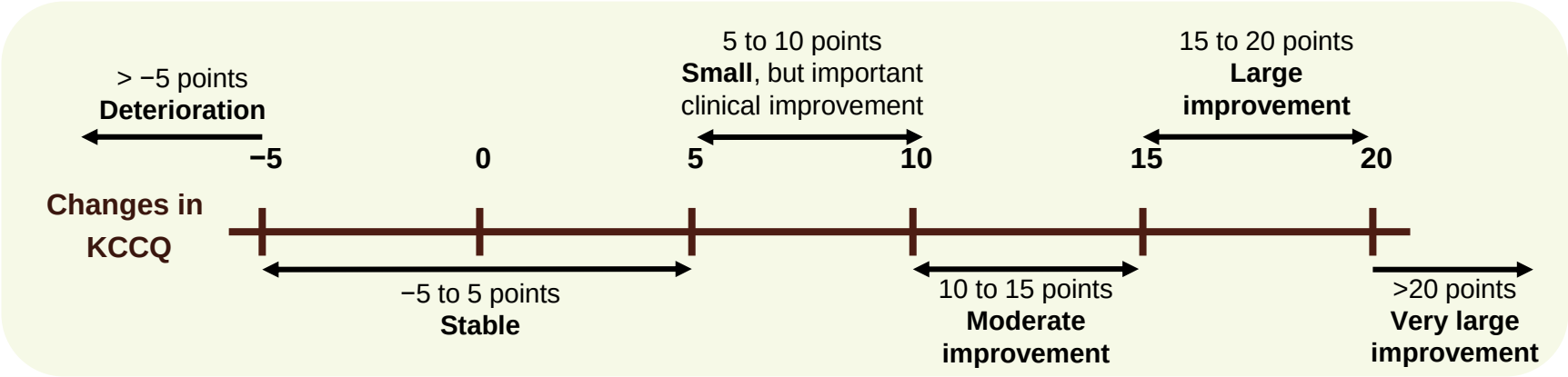
- **23 items that measure 5 clinically relevant domains**
  - Physical Limitation
  - Symptoms (SoB, Fatigue):
    - Frequency
    - Severity
    - Change
  - Social Limitation
  - Quality of Life
  - Self-Efficacy

- **Represents the *patient's* perspective of their heart failure**
- **Established validity, reliability and responsiveness in HCM***
- **Does not measure chest pain – Captured by the Seattle Angina Questionnaire**

* Nassif et al., *JACC Heart Fail*, 2022, 10(8):531-539
SoB, shortness of breath.

Analytic Approach

- Linear regression of 24-week change in KCCQ-OSS/SAQ-SS, adjusted for baseline score and randomization strata (beta-blocker use, CPET modality).
- Responder analyses by clinically important categories of change to support clinical interpretability of mean treatment effects*.



- Minimal missing data (<3%) required no imputation

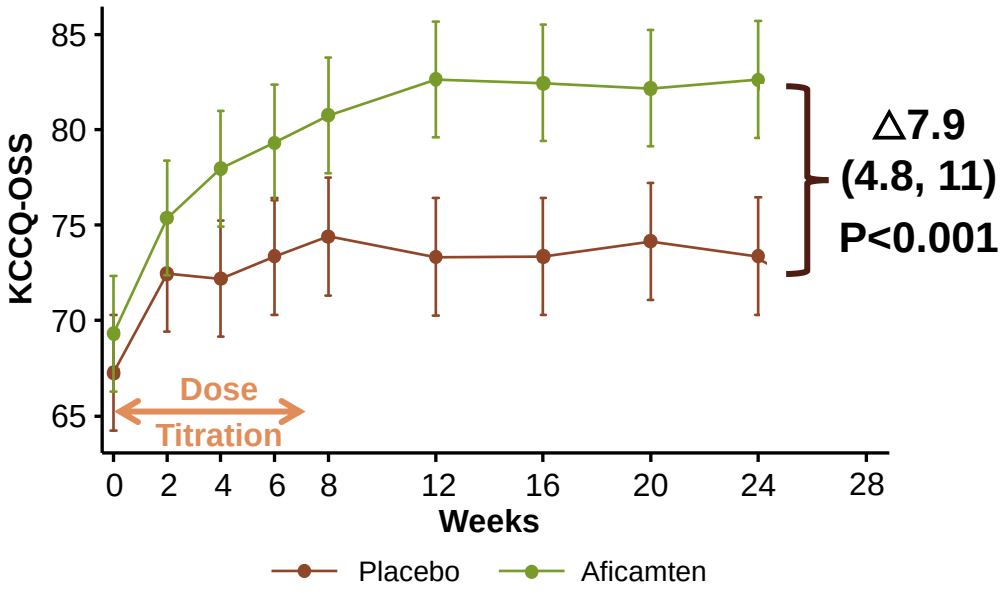
* Nassif et al., *JACC Heart Fail*, 2022, 10(8):531-539.
KCCQ-OSS, KCCQ Overall Summary Score; SAQ-SS, Seattle Angina Questionnaire – Summary Score.

Well-Balanced Baseline Characteristics

	Placebo (n=140)	Aficamten (n=142)
Age (years)	59.0 ± 13.4	59.2 ± 12.6
Female sex	59 (42.1)	56 (39.4)
White	115 (82.1)	108 (76.1)
North America	45 (32.1)	49 (34.5)
Hypertension	70 (50.0)	75 (52.8)
Known gene mutation	25 (17.9)	24 (16.9)
Family History of HCM	34 (24.3)	41 (28.9)
Paroxysmal atrial fibrillation	20 (14.3)	21 (14.8)
BMI, kg/m^2	28.2 ± 3.7	28.0 ± 3.8
Baseline beta-blocker use	87 (62.1)	86 (60.6)
Baseline calcium channel blocker use	46 (32.9)	51 (35.9)
Baseline disopyramide use	20 (14.3)	16 (11.3)
Baseline NT-proBNP, pg/mL, median (range)	692 (335, 1795)	818 (377, 1630)
pVO_2, mL/kg/min	18.6 ± 4.5	18.4 ± 4.4
LVEF %	75 ± 6	75 ± 5
LVOT gradient at rest	55 ± 32	55 ± 27
LV maximal wall thickness, cm	2.10 ± 0.30	2.07 ± 0.30
KCCQ-OSS	**67.3 ± 18.8**	**69.3 ± 20.1**
SAQ-SS	**72.4 ± 18.3**	**72.0 ± 21.0**

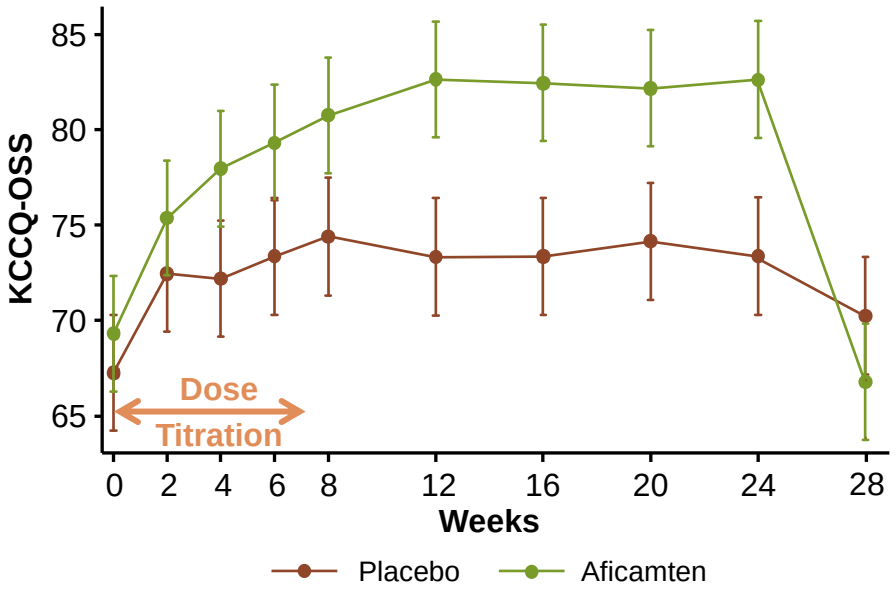
Unless specified, means (±SD) presented; BMI, body mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Mean KCCQ-OSS over Time



NNT, number needed to treat.

Mean KCCQ-OSS over Time



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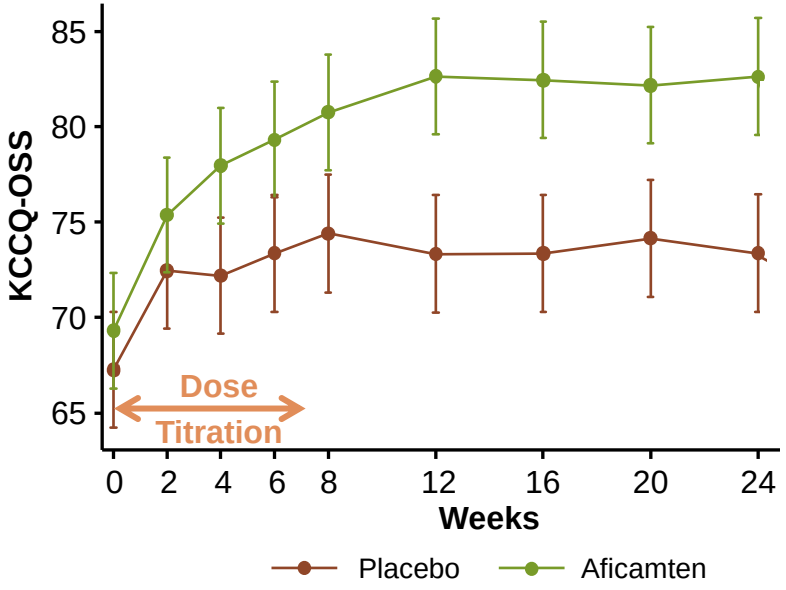
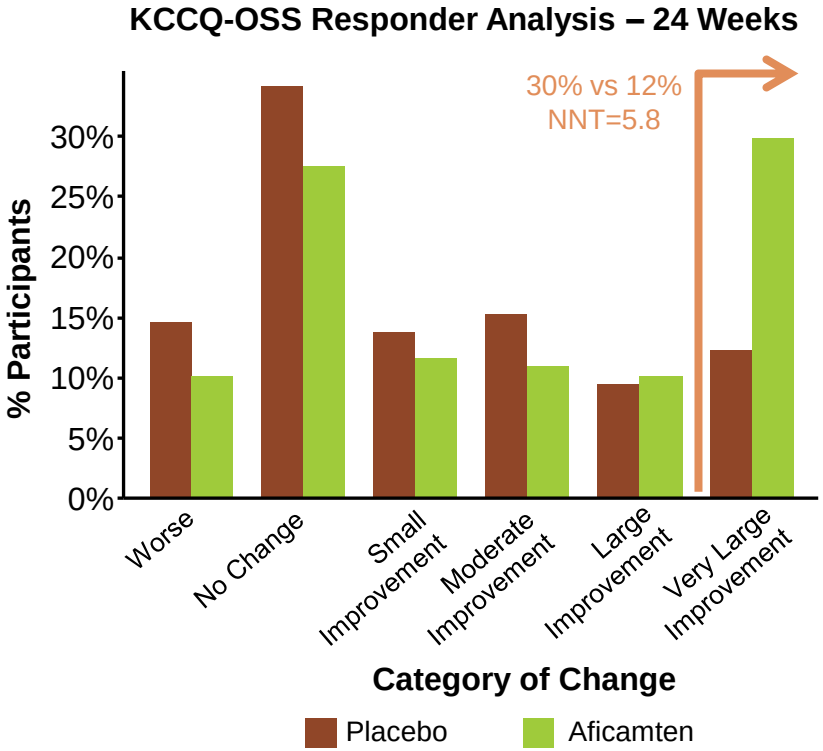
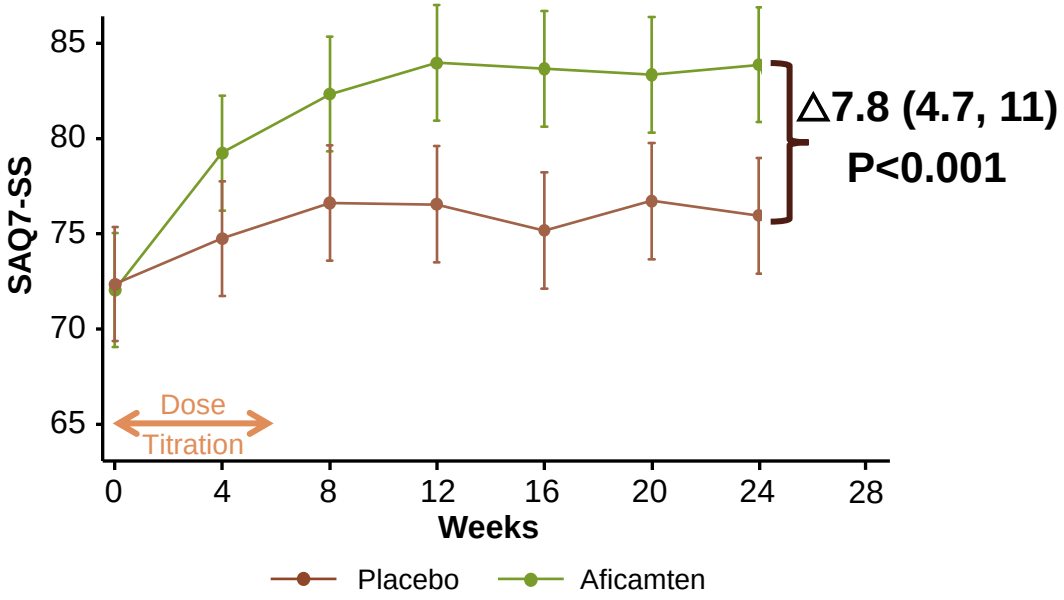


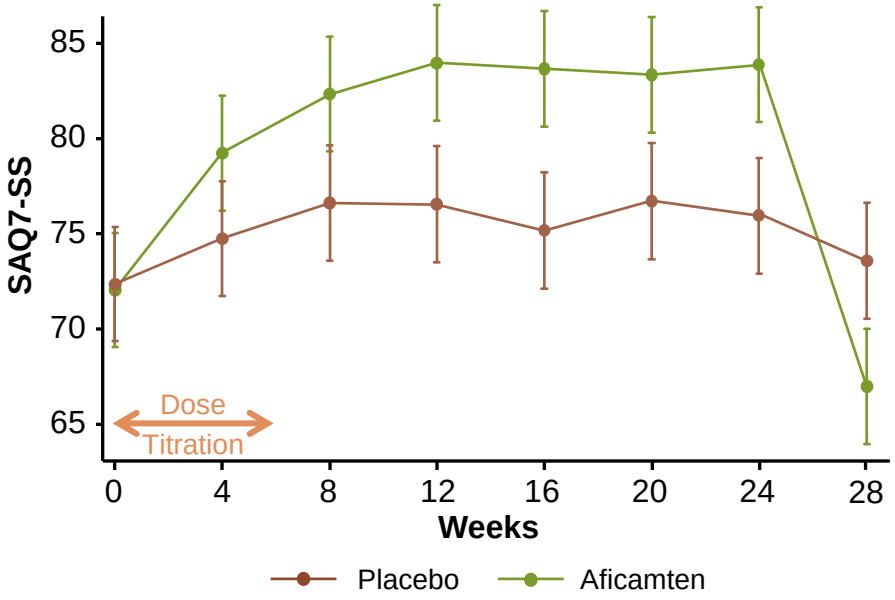


NNT, number needed to treat.

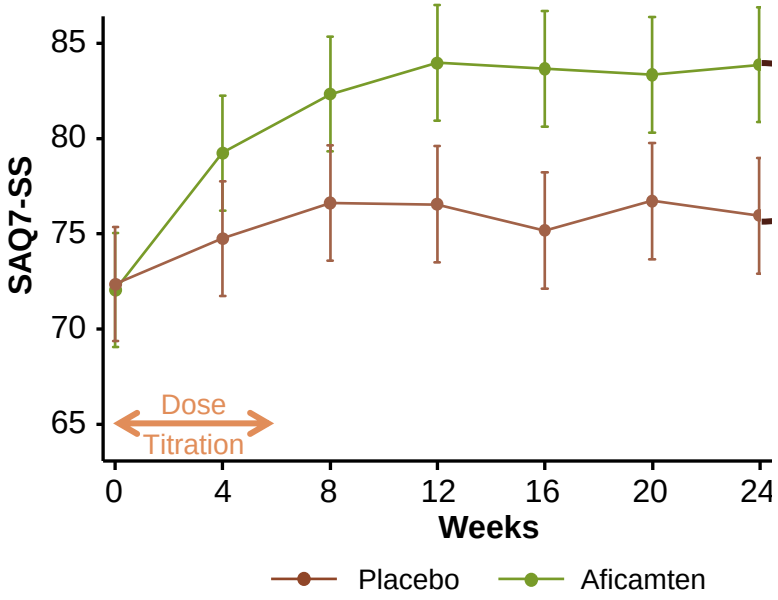
Mean SAQ-SS over Time

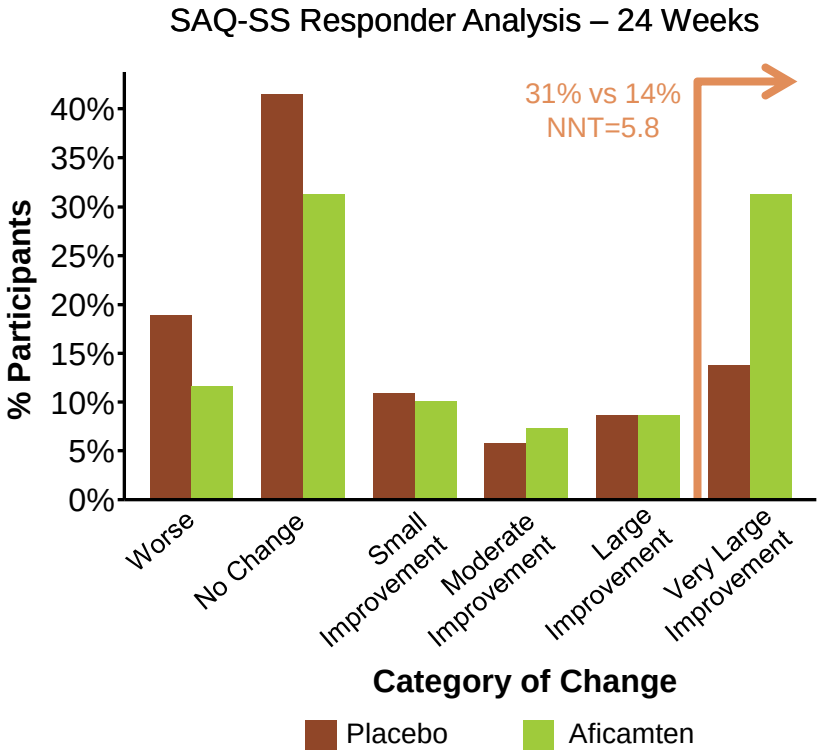


Mean SAQ-SS over Time



Mean SAQ-SS over Time





Limitations

- **SEQUOIA's inclusion criteria may limit generalizability**
  - Further research in non-obstructive HCM is needed
    - ACACIA trial ongoing
- **Some manifestations of HCM (e.g., lightheadedness and palpitations) not captured**
  - KCCQ is highly correlated with HCM symptoms not captured by KCCQ
  - SAQ provides robust quantification of chest pain and its impact on patients' lives
- **Longer-term benefits of aficamten require further study**
  - FOREST-HCM ongoing

Conclusions

- **Aficamten Significantly Improves Patients' Health Status – Their Symptoms, Function and Quality of Life**
  - NNT <6 for 1 patient to experience a marked (>20 points on KCCQ/SAQ) benefit
- **No Meaningful Heterogeneity in Treatment Benefits**
  - Including by severity of oHCM or background therapy
- **Aficamten is a Promising Option to Improve Care for oHCM**
  - Titration based on site interpretation of echocardiograms, supports generalizability
  - Short half-life and excellent safety profile
  - Expands treatment options to those outside specialized HCM centers that offer septal reduction treatment

Acknowledgments

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Effect of Aficamten on Health Status Outcomes in Obstructive Hypertrophic Cardiomyopathy

Results from SEQUOIA-HCM

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ABSTRACT

BACKGROUND A primary goal in treating obstructive hypertrophic cardiomyopathy (oHCM) is to improve patients' health status: their symptoms, function, and quality of life. The health status benefits of aficamten, a novel cardiac myosin inhibitor, have not been comprehensively described.

OBJECTIVES This study sought to determine the effect of aficamten on patient-reported health status, including symptoms of fatigue, shortness of breath, chest pain, physical and social limitations, and quality of life.

METHODS SEQUOIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM) randomized symptomatic adults with oHCM to 24 weeks of aficamten (n = 142) or placebo (n = 140), followed by a 4-week washout. The Kansas City Cardiomyopathy Questionnaire (KCCQ) and Seattle Angina Questionnaire 7-item (SAQ7) were serially administered. Changes in mean KCCQ–Overall Summary Score (KCCQ-OSS) and SAQ7–Summary Score (SAQ7-SS) from baseline to 24 weeks and following treatment withdrawal were compared using linear regression adjusted for baseline scores and randomization strata. Proportions of patients with clinically important changes were compared.

RESULTS Among 282 participants, the mean age was 59 ± 13 years, 115 (41%) were female, and 223 (79%) were White. Baseline KCCQ-OSS (69.3 ± 20.1 vs 67.3 ± 18.8) and SAQ7-SS (72.0 ± 21.0 vs 72.4 ± 18.3) were similar between aficamten and placebo groups. Treatment with aficamten, compared with placebo, improved both the mean KCCQ-OSS (13.3 ± 16.3 vs 6.1 ± 12.6; mean difference: 7.9; 95% CI: 4.8-11.0; $P < 0.001$) and SAQ7-SS (11.6 ± 17.4 vs 3.8 ± 14.4; mean difference: 7.8; 95% CI: 4.7-11.0; $P < 0.001$) at 24 weeks, with benefits emerging within 4 weeks. No heterogeneity in treatment effect was found across subgroups. A much larger proportion of participants experienced a very large health status improvement (≥20 points) with aficamten vs placebo (KCCQ-OSS: 29.7% vs 12.4%, number needed to treat: 5.8; SAQ7-SS: 31.2% vs 13.9%, number needed to treat: 5.8). Participants' health status worsened significantly more after withdrawal from aficamten than placebo (KCCQ-OSS: −16.2 ± 19.0 vs −3.0 ± 9.6; $P < 0.001$; SAQ7-SS: −17.4 ± 21.4 vs −2.5 ± 13.3), further confirming a causal effect of aficamten.

CONCLUSIONS In patients with symptomatic oHCM, treatment with aficamten resulted in markedly improved health status, including significant improvement in chest pain-related health status, than placebo. (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM [SEQUOIA-HCM]; NCT05186818) (JACC. 2024;■:■-■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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