Impact of Aficamten on Disease and Symptom Burden in Obstructive Hypertrophic Cardiomyopathy:

Results from SEQUOIA-HCM

Martin S. Maron,[1] Ahmad Masri, Michael E. Nassif, Roberto Barriales-Villa, Theodore P. Abraham, Michael Arad, Nuno Cardim, Lubna Choudhury, Brian Claggett, Caroline J. Coats, Hans-Dirk Düngen, Pablo Garcia-Pavia, Albert A. Hagège, James L. Januzzi, Ian Kulac, Matthew M.Y. Lee, Gregory D. Lewis, Chang-Sheng Ma, Michelle Michels, Artur Oreziak, Anjali T. Owens, John A. Spertus, Scott Solomon, Jacob Tfelt-Hansen, Marion van Sinttruije, Josef Veselka, Hugh C. Watkins, Daniel L. Jacoby, Stephen, B. Heitner, Stuart Kupfer, Fady I. Malik, Lisa Meng, Amy Wohltman, Iacopo Olivotto, on behalf of the SEQUOIA-HCM Investigators

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Heart Failure Society of America (HFSA) Annual Scientific Meeting
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Learning Objectives

- After participating in this plenary session, attendees should be able to:
  - Explain the four clinically relevant outcomes that characterize response to aficamten after 24 weeks of treatment.
  - Discuss the broad clinical efficacy of aficamten for the treatment of patients with symptomatic obstructive HCM.

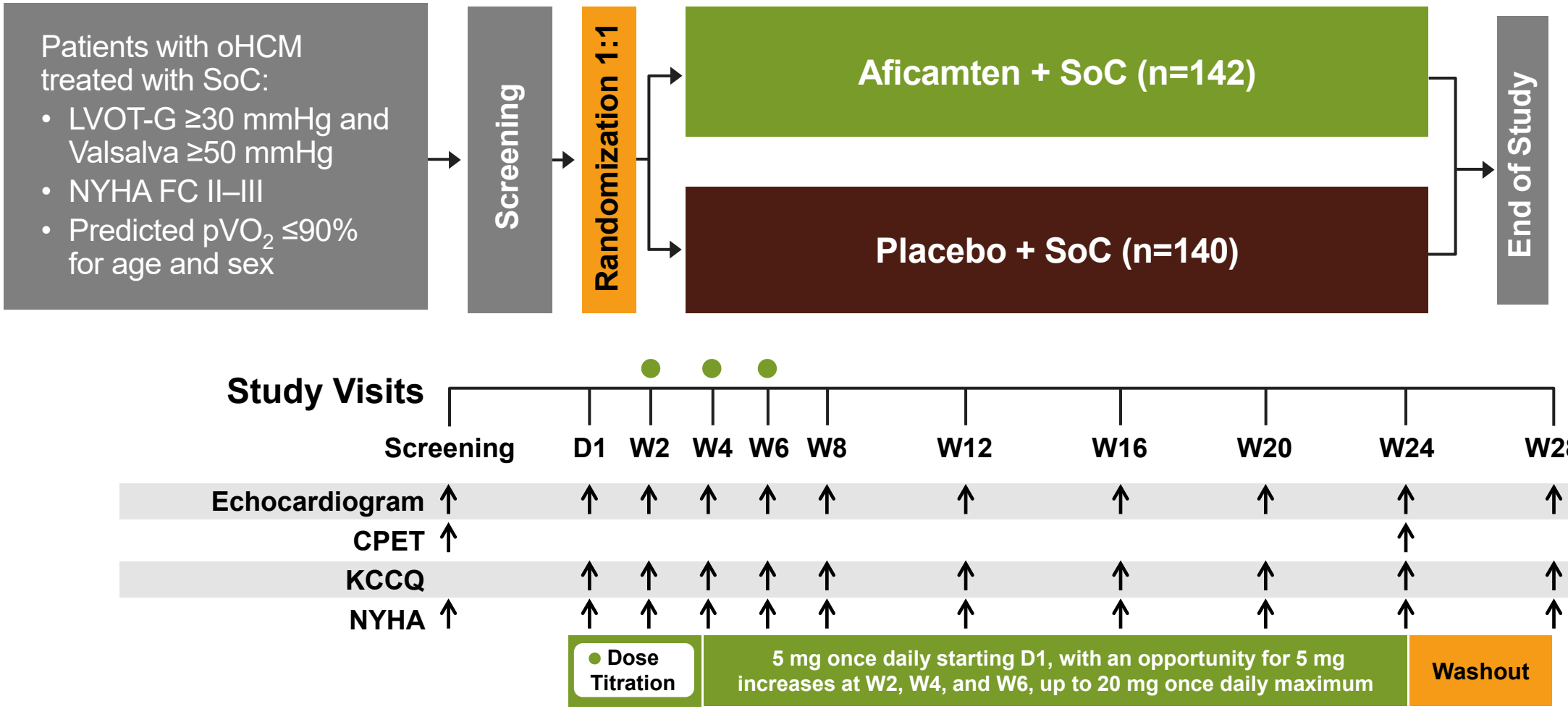
Background

- In obstructive hypertrophic cardiomyopathy (oHCM), left ventricular outflow tract obstruction is the predominant mechanism responsible for limiting symptoms and other adverse outcomes.
- Historically, efficacy of therapeutic interventions has been defined by reduction in outflow gradients and improvement in symptoms (NYHA).
- Recently, KCCQ scores have been associated with enhanced sensitivity when assessing clinically relevant changes in symptom burden/quality of life.[1]
  - Exercise capacity and biomarkers are other measures that reflect a favorable impact of treatment.[2,3]
- Aficamten, a novel cardiac myosin inhibitor, reduces outflow gradients and enhances functional capacity in oHCM.[4]
- However, a comprehensive analysis of the efficacy of aficamten across key clinical outcomes has not been reported.

KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; LVOT-G, LVOT, left ventricular outflow tract gradient.

1. Sherrod CF 4th, et al. *J Am Coll Cardiol* 2024:S0735-1097(24)08166-X; *in press.* **2.** Lee MMY, et al. *JAMA Cardiol* 2024:e242781; online ahead of print.
3. Coats CJ et al. *Eur Heart J* 2024:ehae590; online ahead of print. **4.** Maron MS, et al. *N Engl J Med* 2024;390:1849-61.

Methods: SEQUOIA-HCM Study Design



CPET, cardiopulmonary exercise testing; D, day; NYHA FC, NYHA functional class; pVO_2, peak oxygen consumption; SoC, standard of care; W, week.
Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199-215.

Methods: Endpoints

- The primary objective of this study was to characterize the response achieved with aficamten vs placebo, at 24 weeks and also compared with baseline, for four clinically relevant outcomes:

1. **Complete Hemodynamic Response**: resting and Valsalva LVOT-G <30 mmHg and <50 mmHg, respectively.
   - LVOT-G <50 mmHg is associated with excellent long-term survival.
2. **Relief of Limiting Symptoms:** ≥1 change in NYHA class and/or ≥10-point increase in the KCCQ-CCS.
   - Increases in KCCQ are associated with a substantial reduction in CV adverse events across HF populations, with a ≥10-point change considered a moderate to large improvement.
3. **Enhanced Exercise Capacity**: ≥1.5 mL/kg/min change in pVO_2.
   - This pVO_2 cut-off exceeds the threshold for a clinically meaningful change.
4. **Cardiac Biomarker Response:** ≥50% reduction in serum NT-proBNP levels.
   - Similar magnitude change associated with enhanced survival in a non-HCM population.

CV, cardiovascular; HF, heart failure; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Methods: Endpoints

- Treatment effect was also assessed per a pre-specified analysis of patients who achieved:

Improvement in Limiting Symptoms and Exercise:

≥1.5 mL/kg/min change in pVO_2 and ≥1 change in NYHA class;

or

≥3.0 mL/kg/min change in pVO_2 and no worsening in NYHA class

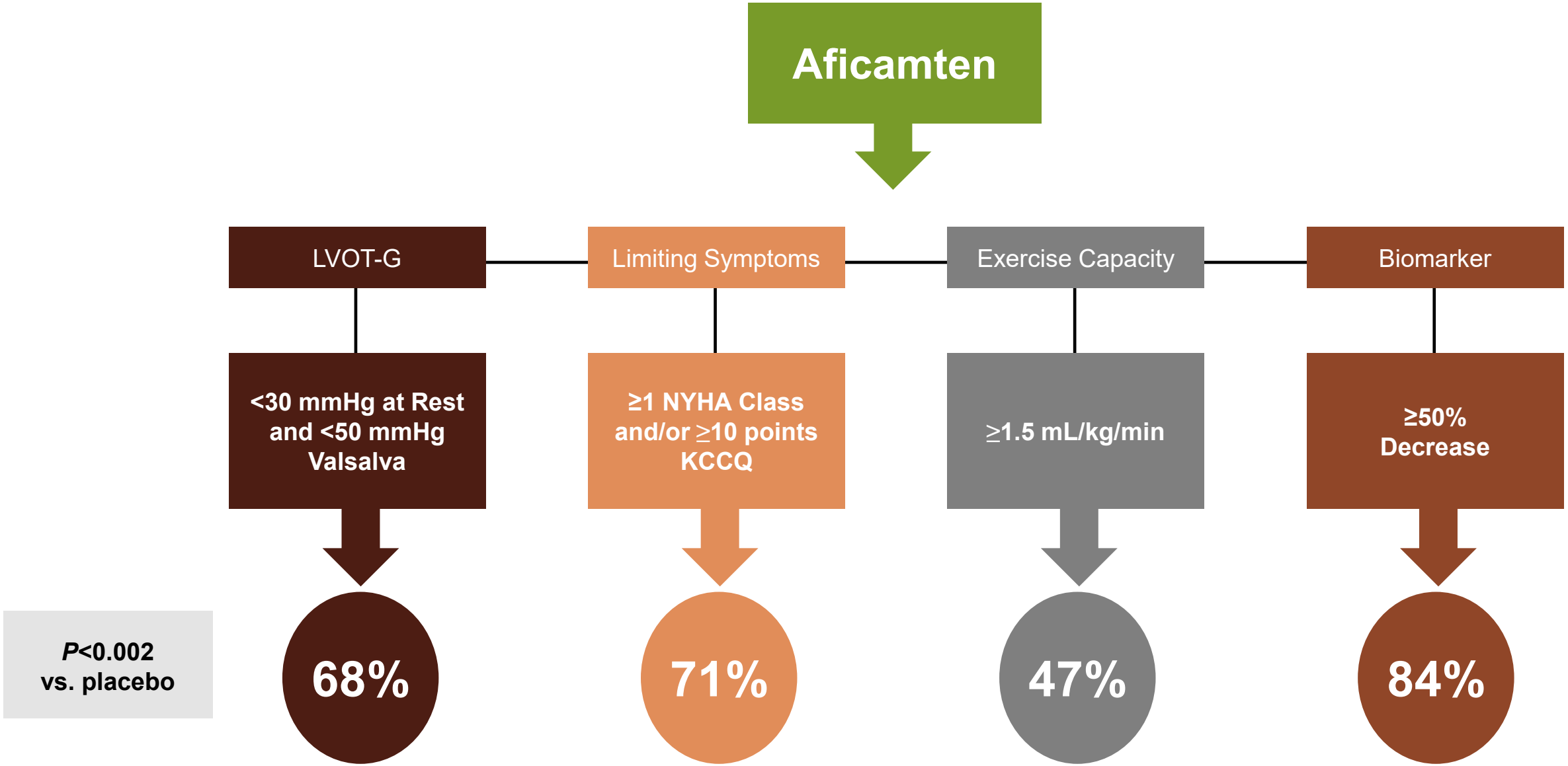
Guideline Eligibility for SRT:

Week 24 vs those eligible at baseline

(NYHA class III or IV and LVOT-G ≥50 mmHg at rest or Valsalva)

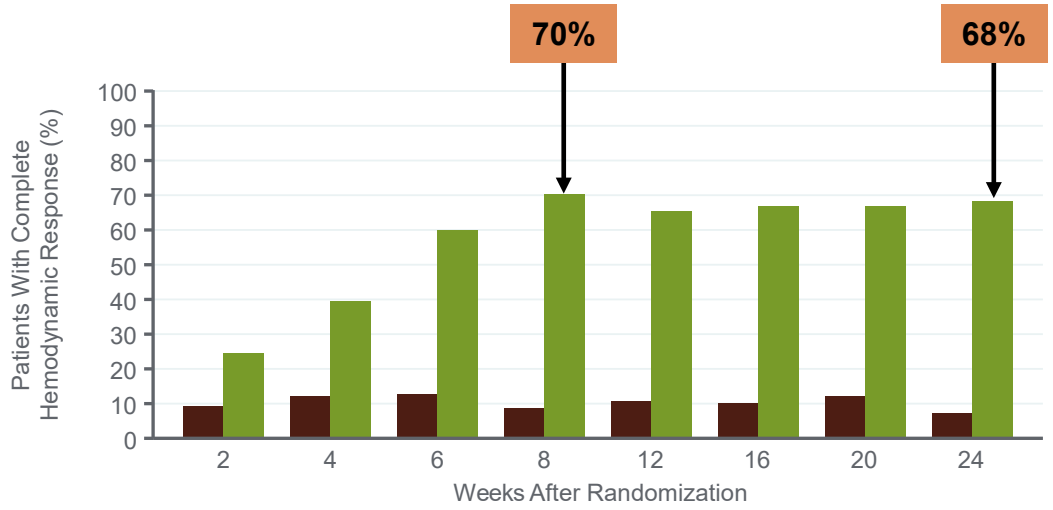
SRT, septal reduction therapy.

SEQUOIA-HCM Responder Analysis

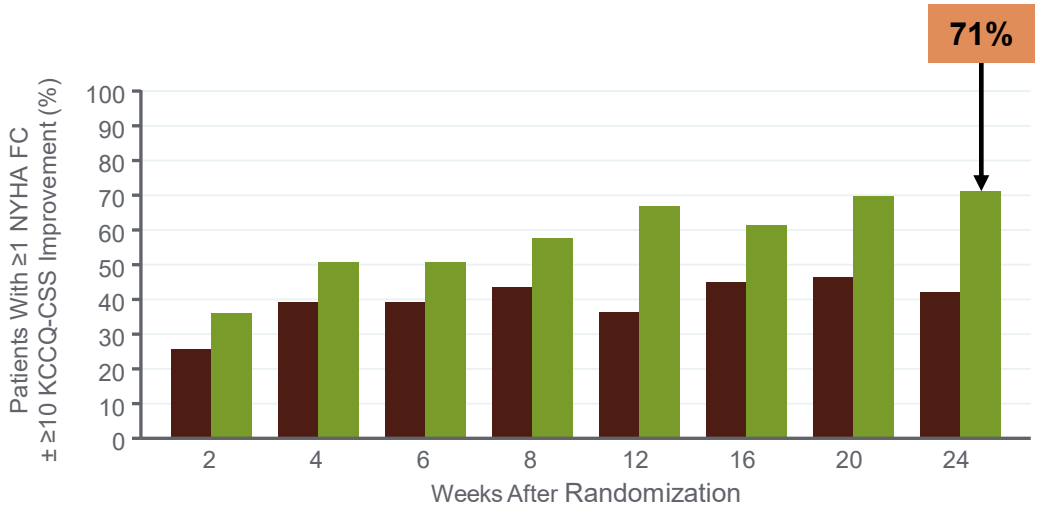


Clinical Response Measures in Patients with oHCM from Baseline to Week 24

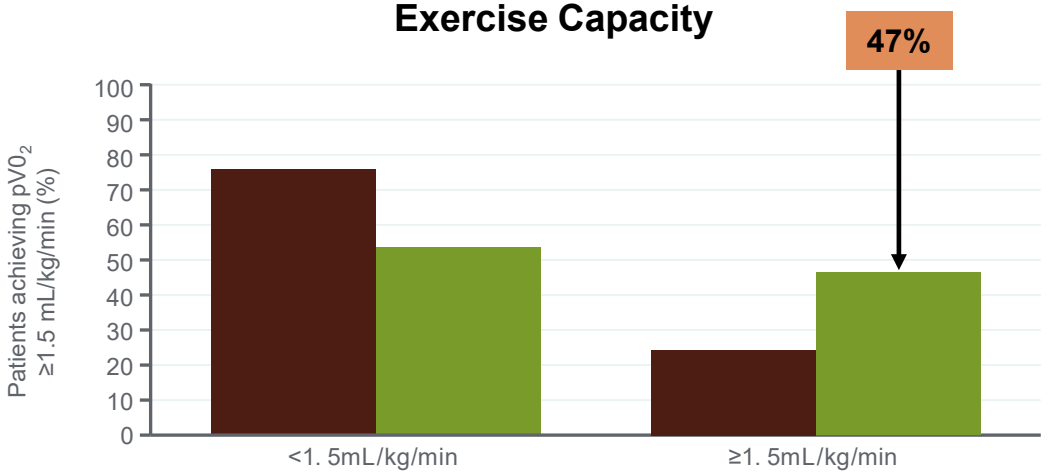
Complete Hemodynamic Response



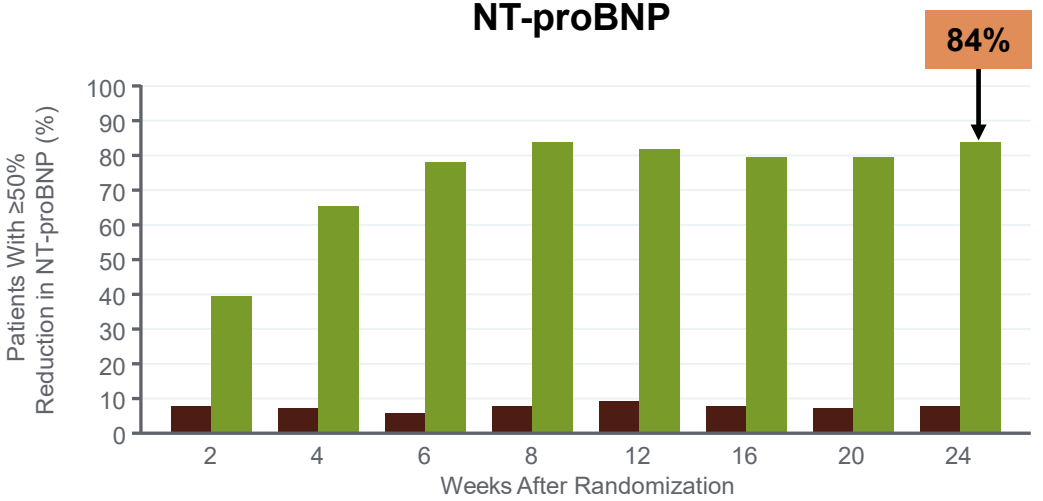
Improvement in Limiting Symptoms



Exercise Capacity

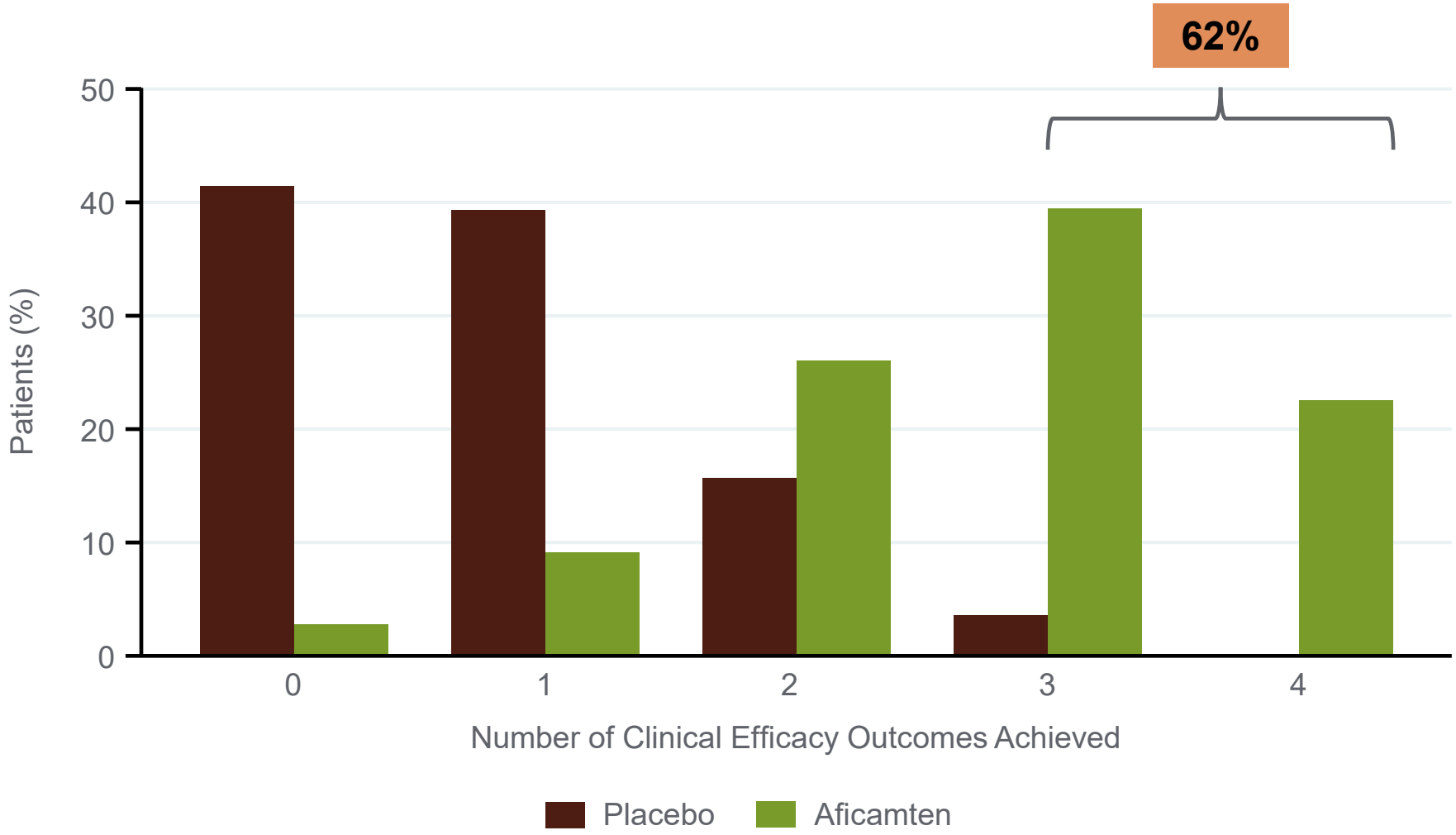


NT-proBNP



Placebo Aficamten

Proportion of Patients with oHCM Who Achieved ≥ 1 Clinically Relevant Outcome on Aficamten vs Placebo



Impact of Treatment Effect Relative to Placebo

Outcome	Placebo n (%)	Aficamten n (%)	Risk Difference (95% CI)	NNT (95% CI)
Complete Hemodynamic Response	10 (7)	97 (68)	61% (52, 70)	1.6
Improvement in HF Symptoms	59 (42)	101 (71)	29% (18, 40)	3.5
Enhanced Exercise Capacity	34 (24)	66 (46.5)	22% (11, 33)	4.5
Reduction in NT-proBNP	11 (8)	119 (84)	76% (68, 84)	1.3

NNT, number needed to treat.

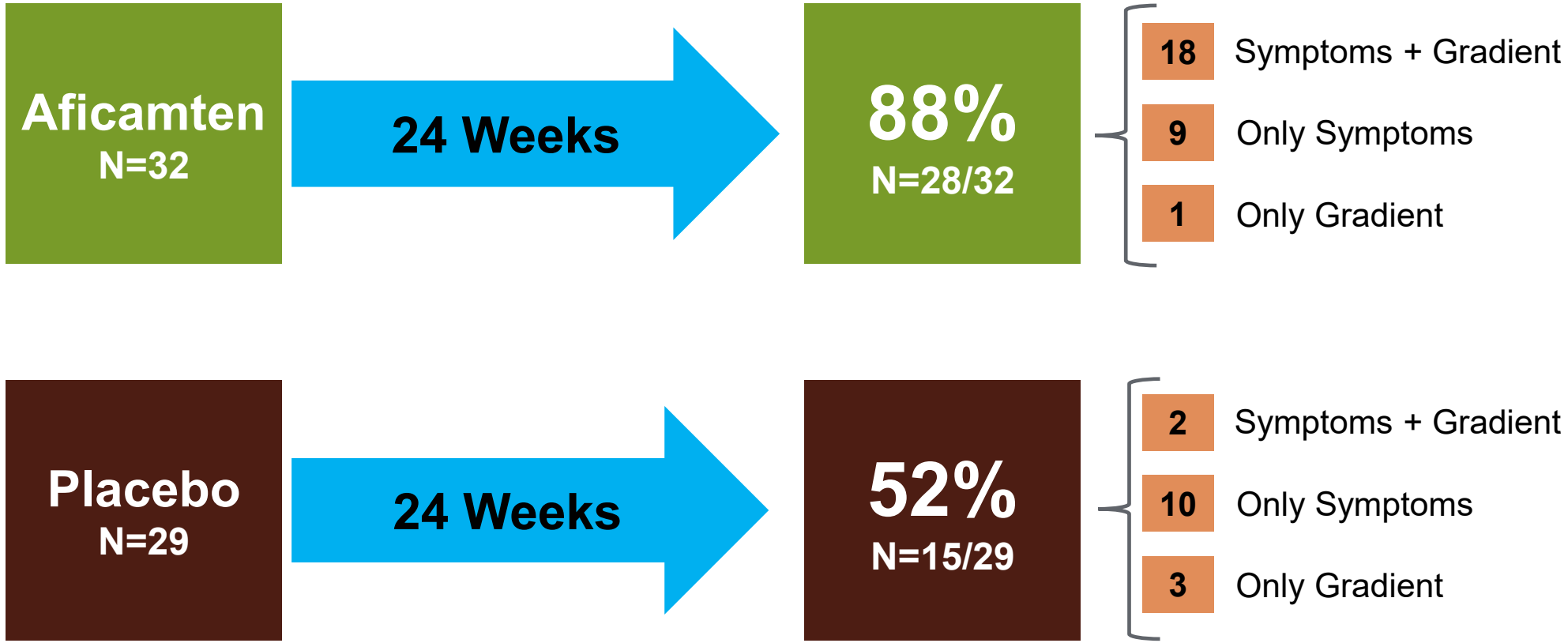
Change with Aficamten in Exercise Capacity by pVO_2 and Limiting Symptoms with NYHA Functional Class

Outcome	Placebo n=140	Aficamten n=142
≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA class improvement or ≥3.0 mL/kg/min increase in pVO_2 and no worsening of NYHA class, n (%)	19 (14)	60 (42)
≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA class improvement, n (%)	9 (6)	44 (31)
≥3.0 mL/kg/min increase in pVO_2 and no worsening of NYHA class, n (%)	13 (9)	37 (26)
≥3.0 mL/kg/min increase in pVO_2 and ≥1 NYHA class improvement, n (%)	3 (2)	21 (15)
Common rate difference (vs placebo)	–	29
95% CI common rate difference	–	(19–39)
P value	–	<0.0001

Change in Eligibility for SRT for Patients on Aficamten vs Placebo

Guideline Eligible For SRT
(Gradient >50 mmHg and NYHA Class III or IV)

Guideline *Ineligible* For SRT
(Gradient <50 mmHg and/or NYHA Class I or II)



Summary

- Over a relatively short treatment period, nearly all patients (97%) on aficamten experienced a clinically meaningful improvement in ≥1 clinically relevant outcome measure, including:
  - Complete hemodynamic response
  - Relief in limiting symptoms
  - Enhanced exercise capacity
  - Significant decrease in NT-proBNP

- Combined effect of aficamten on improving symptomatic status and hemodynamics converted most patients who were guideline eligible for SRT at baseline to no longer meeting those criteria

- These findings underscore the broad clinical efficacy of aficamten for the treatment of patients with symptomatic oHCM, including those eligible for SRT

Acknowledgments

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- Participants and their families
- Investigators and study site staff
- Data Monitoring Committee members
- Steering Committee members: Gregory D. Lewis, Theodore Abraham, Michael Arad, Nuno Cardim, Lubna Choudhury, Caroline J. Coats, Milind Desai, Hans-Dirk Düngen, Pablo Garcia-Pavia, Albert A. Hagège, Carolyn Y. Ho, James L. Januzzi, Christopher Kramer, Raymond Kwong, Matthew M.Y. Lee, Chang-Sheng Ma, Martin S. Maron, Ahmad Masri, Michelle Michels, Iacopo Olivotto, Artur Oreziak, Anjali T. Owens, Sara Saberi, Scott D. Solomon, John A. Spertus, Jacob Tfelt-Hansen, Marion van Sinttruije, Josef Veselka, and Hugh C. Watkins

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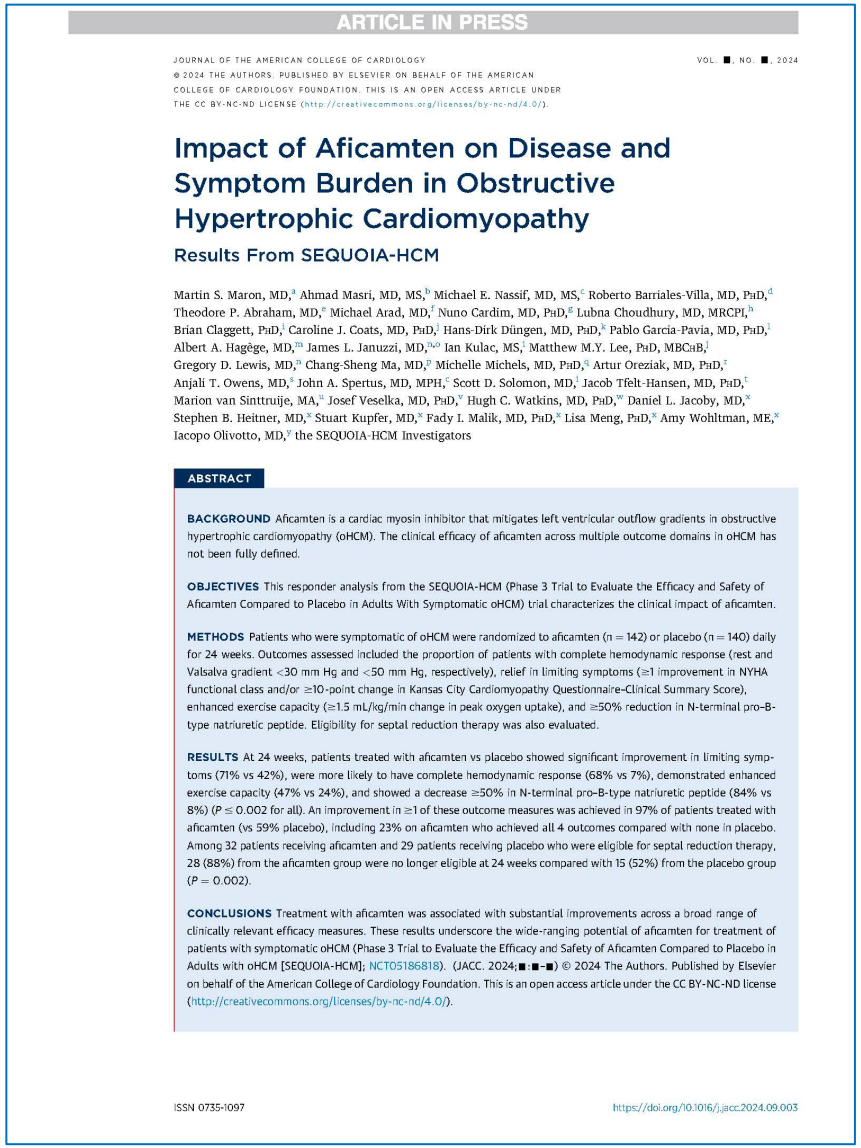

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ABSTRACT

BACKGROUND Aficamten is a cardiac myosin inhibitor that mitigates left ventricular outflow gradients in obstructive hypertrophic cardiomyopathy (oHCM). The clinical efficacy of aficamten across multiple outcome domains in oHCM has not been fully defined.

OBJECTIVES This responder analysis from the SEQUOIA-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults With Symptomatic oHCM) trial characterizes the clinical impact of aficamten.

METHODS Patients who were symptomatic of oHCM were randomized to aficamten (n = 142) or placebo (n = 140) daily for 24 weeks. Outcomes assessed included the proportion of patients with complete hemodynamic response (rest and Valsalva gradient <30 mm Hg and <50 mm Hg, respectively), relief in limiting symptoms (≥1 improvement in NYHA functional class and/or ≥10-point change in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score), enhanced exercise capacity (≥1.5 mL/kg/min change in peak oxygen uptake), and ≥50% reduction in N-terminal pro-B-type natriuretic peptide. Eligibility for septal reduction therapy was also evaluated.

RESULTS At 24 weeks, patients treated with aficamten vs placebo showed significant improvement in limiting symptoms (71% vs 42%), were more likely to have complete hemodynamic response (68% vs 7%), demonstrated enhanced exercise capacity (47% vs 24%), and showed a decrease ≥50% in N-terminal pro-B-type natriuretic peptide (84% vs 8%) ($P \leq 0.002$ for all). An improvement in ≥1 of these outcome measures was achieved in 97% of patients treated with aficamten (vs 59% placebo), including 23% on aficamten who achieved all 4 outcomes compared with none in placebo. Among 32 patients receiving aficamten and 29 patients receiving placebo who were eligible for septal reduction therapy, 28 (88%) from the aficamten group were no longer eligible at 24 weeks compared with 15 (52%) from the placebo group ($P = 0.002$).

CONCLUSIONS Treatment with aficamten was associated with substantial improvements across a broad range of clinically relevant efficacy measures. These results underscore the wide-ranging potential of aficamten for treatment of patients with symptomatic oHCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Placebo in Adults with 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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