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**Where Heart Failure Teams Gather
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Global Efficacy of Aficamten in Nonobstructive Hypertrophic Cardiomyopathy: Results From ACACIA-HCM

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Background

- Nonobstructive hypertrophic cardiomyopathy (nHCM) is associated with significant morbidity with no approved treatment
- Aficamten is a CMI targeting excess contractility and diastolic impairment, the predominant mechanism responsible for adverse outcomes in nHCM
- In the ACACIA-HCM trial, aficamten significantly improved outcomes in patients with nHCM vs placebo¹
- To contextualize the observed treatment effects, we performed a responder analysis integrating multiple clinically relevant measures

Methods: ACACIA-HCM Study Design

Patients with symptomatic nHCM:

- NYHA FC II–III
- KCCQ-CSS ≤85
- LVEF ≥60%
- NT-proBNP ≥300 pg/mL
- Resting LVOT gradient <30 mmHg
- Peak Valsalva LVOT gradient <50 mmHg

Screening

Randomization 1:1
N=517

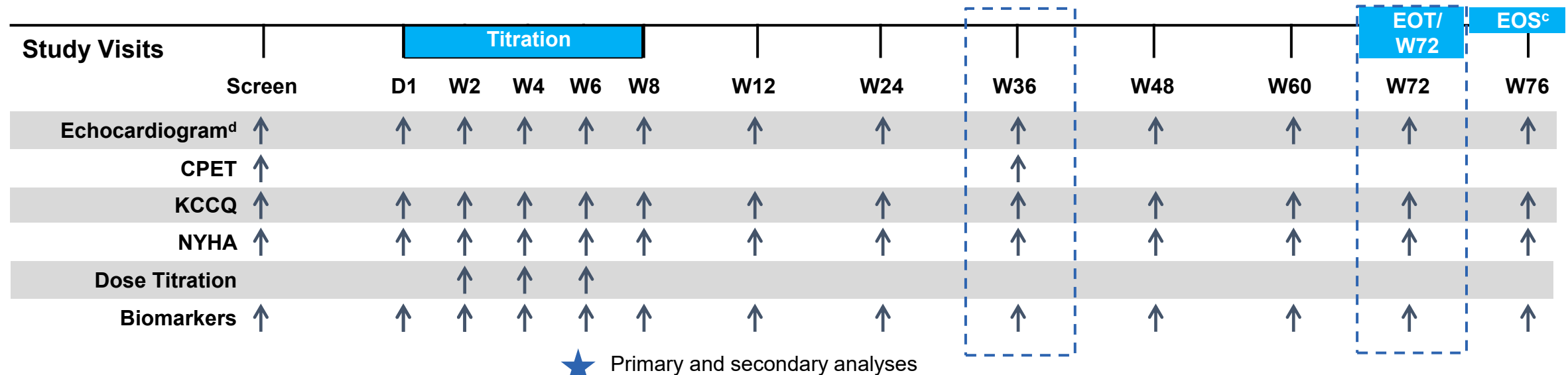
Aficamten (5–20 mg)
n=258

Placebo
n=259

EOS

Part 1^a

Part 2^b

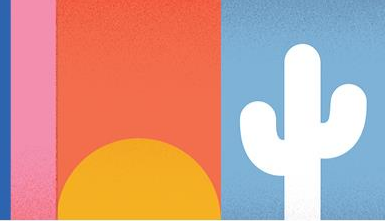


1. Masri A, et al. 2026. Aug 28. *N Engl J Med*. doi: 10.1056/NEJMoa2603021.

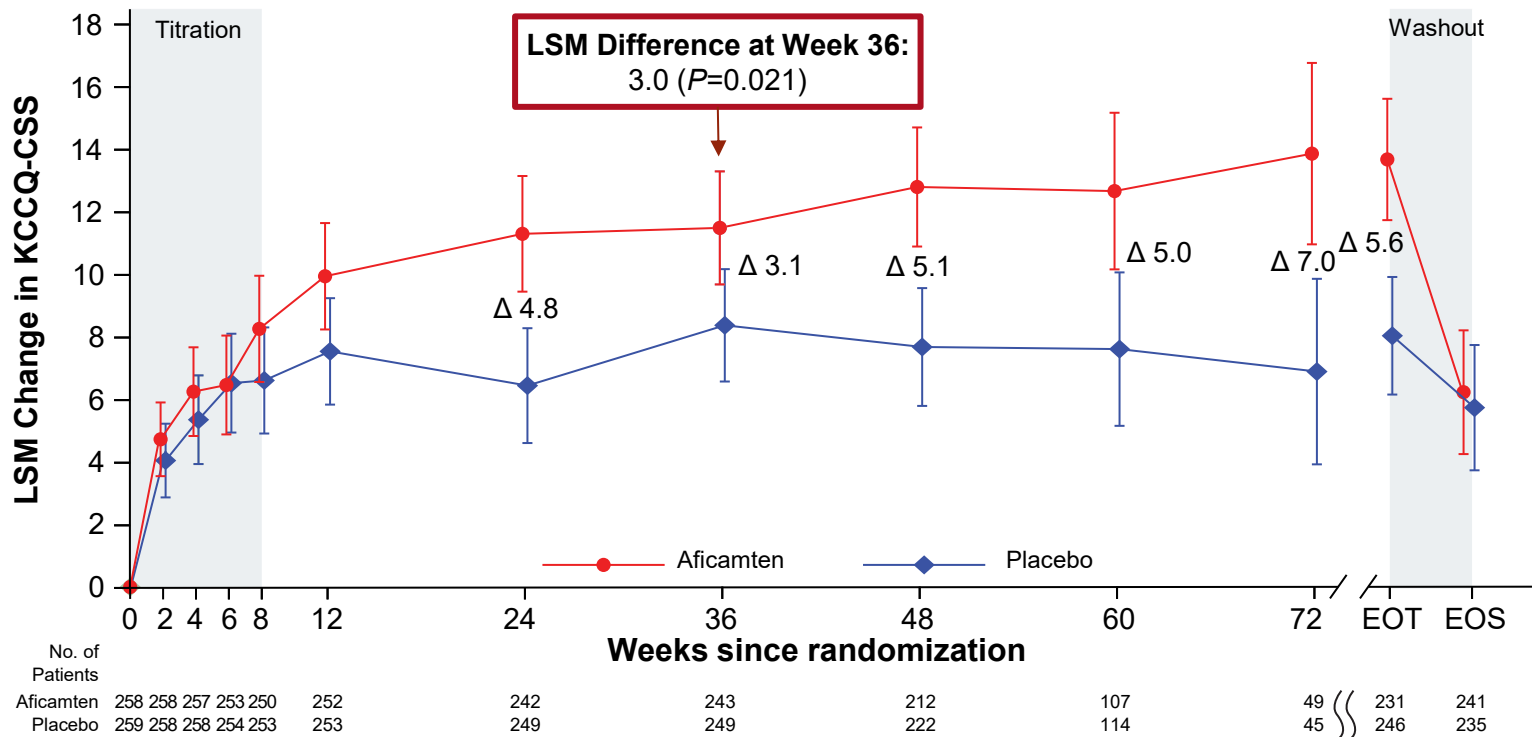
^a Part 1: All patients followed until W36. ^b Part 2: When ≥200 patients reached 52 weeks of treatment, all remaining active-study patients who completed W36 were eligible for an EOT visit followed by an EOS visit. ^c Occurred ≥4 weeks after the last dose of investigational product. ^d Site-read focused echocardiogram for titration visit (sole criterion).

CPET, cardiopulmonary exercise test; D, day; EOS, end of study; EOT, end of treatment; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; nHCM, nonobstructive hypertrophic cardiomyopathy; NYHA FC, New York Heart Association functional class; W, week.

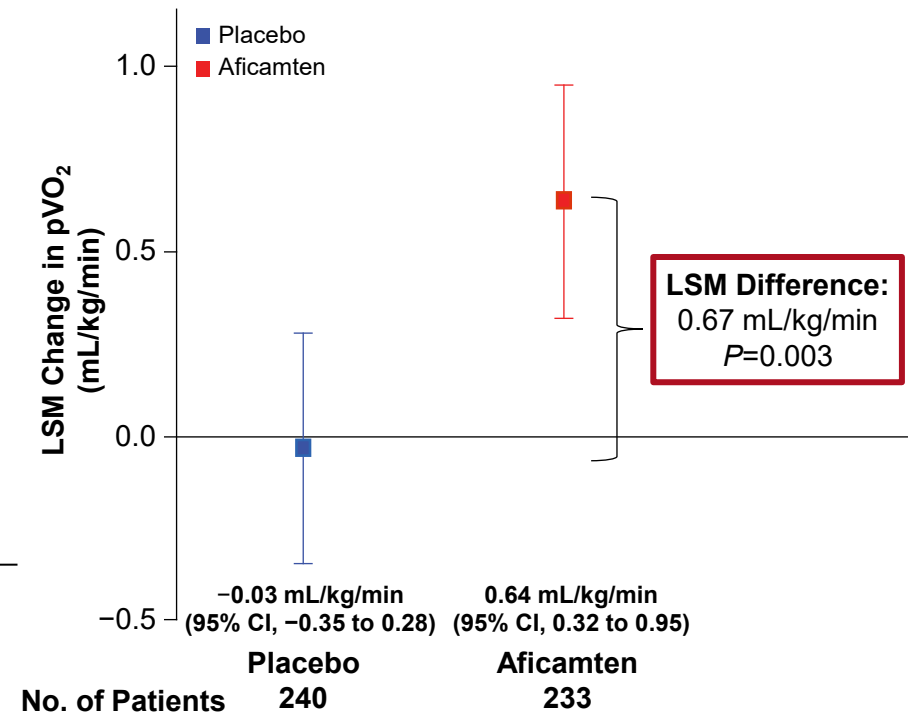
ACACIA-HCM Primary Results: KCCQ-CSS and pVO₂ (Dual Primary endpoint at Week 36)



KCCQ-CSS

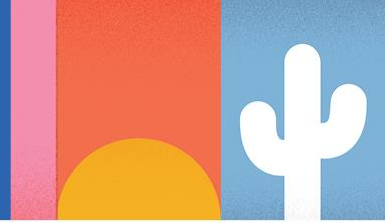


Change in pVO₂



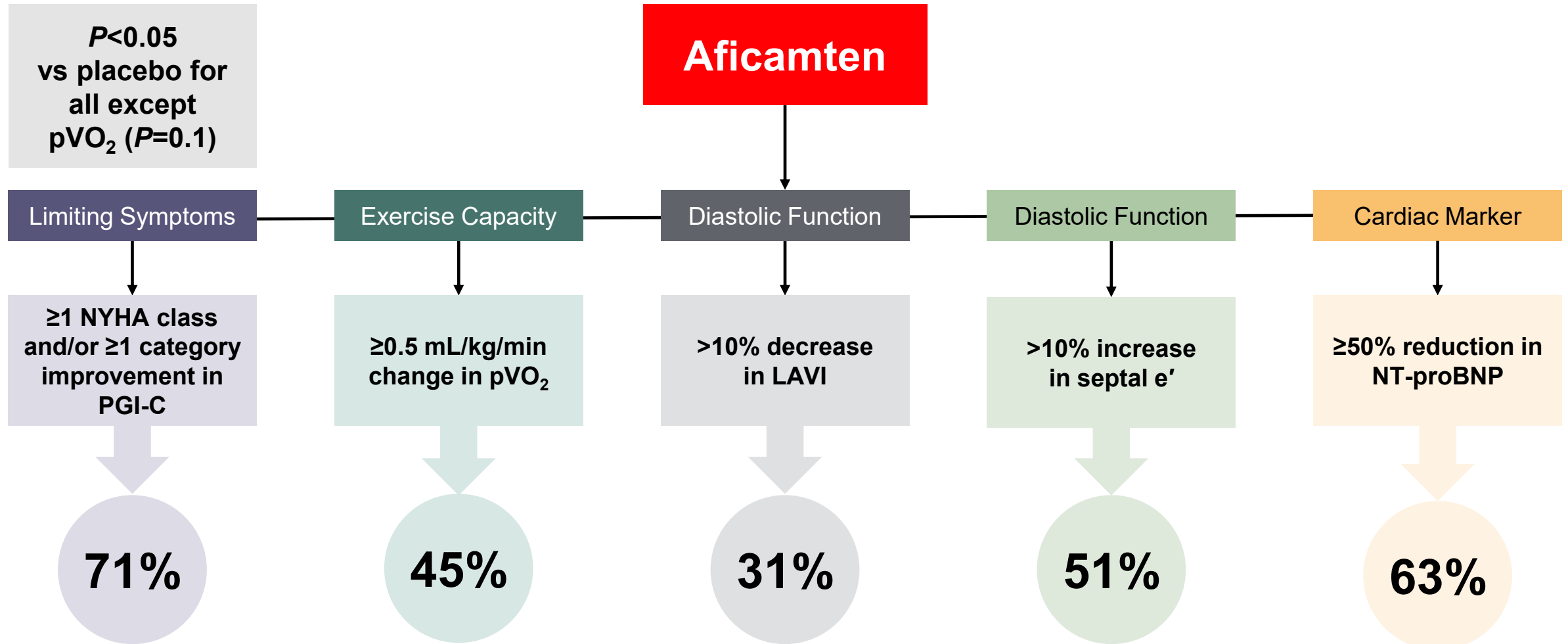
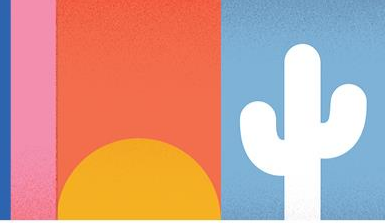
1. Masri A, et al. 2026. Aug 28. *N Engl J Med*. doi: 10.1056/NEJMoa2603021.
KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LSM, least squares mean; pVO₂, peak oxygen volume.

Methods: Endpoints

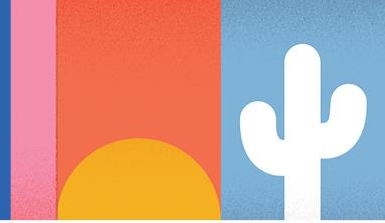


1. **Relief of Limiting Symptoms:** ≥ 1 change in NYHA class and/or reported increase in PGI-C
 - PGI-C is an established anchor to determine clinically meaningful differences in other PROs; a 1-category improvement in PGI-C is considered clinically meaningful
2. **Enhanced Exercise Capacity:** ≥ 0.5 mL/kg/min increase in pVO_2
 - This difference in pVO_2 associated with a clinically meaningful change in patient's perceived symptoms
3. **Diastolic Function:** $>10\%$ decrease in LAVI
 - Similar magnitude change associated with lower risk of adverse CV outcomes
4. **Diastolic Function:** $>10\%$ increase in septal e'
 - Similar magnitude change associated with enhanced survival in an nHCM population
5. **Cardiac Biomarker:** $\geq 50\%$ reduction in NT-proBNP
 - Similar magnitude change associated with improved CV outcomes in an nHCM population

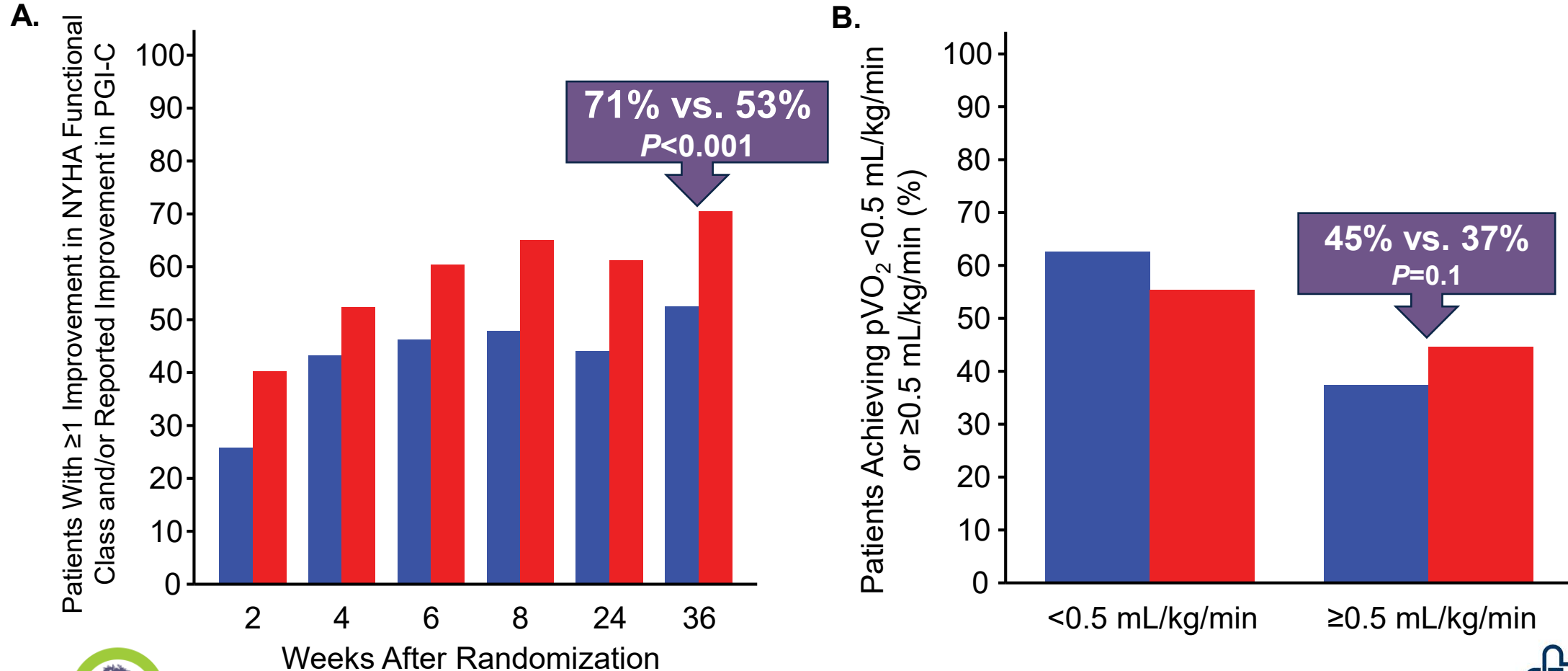
ACACIA-HCM Responder Analysis



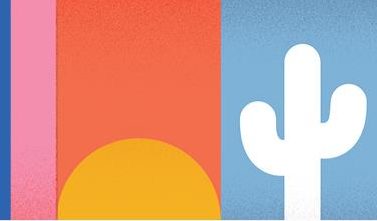
Clinical Response Measures from Baseline to Week 36 in Patients with nHCM



■ Placebo ■ Aficamten

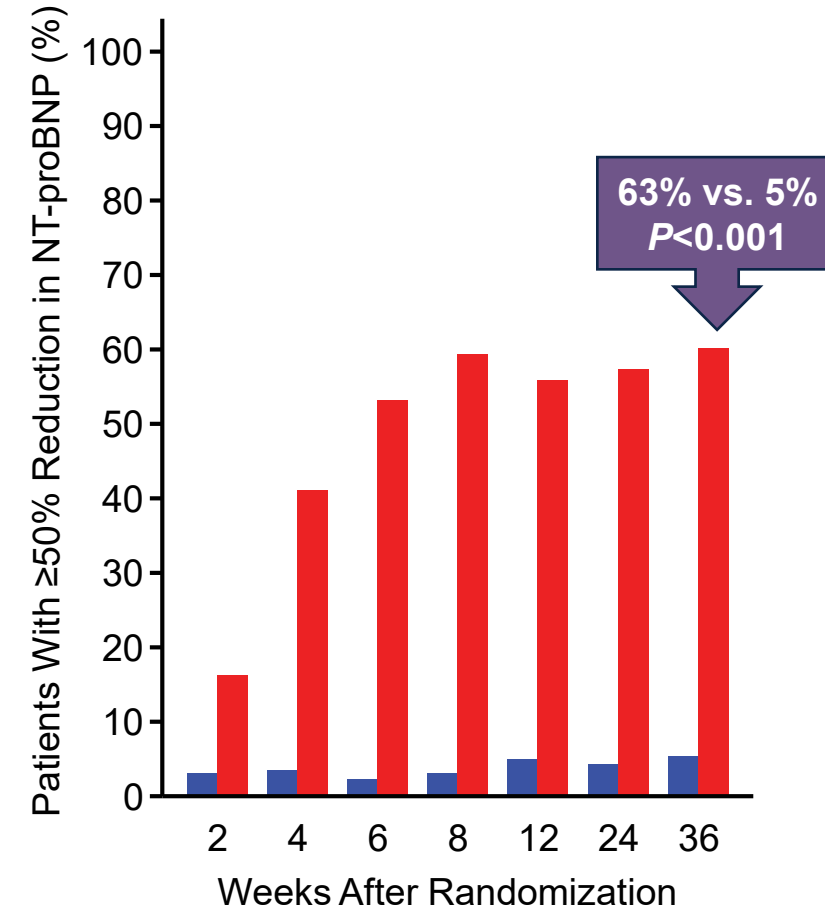
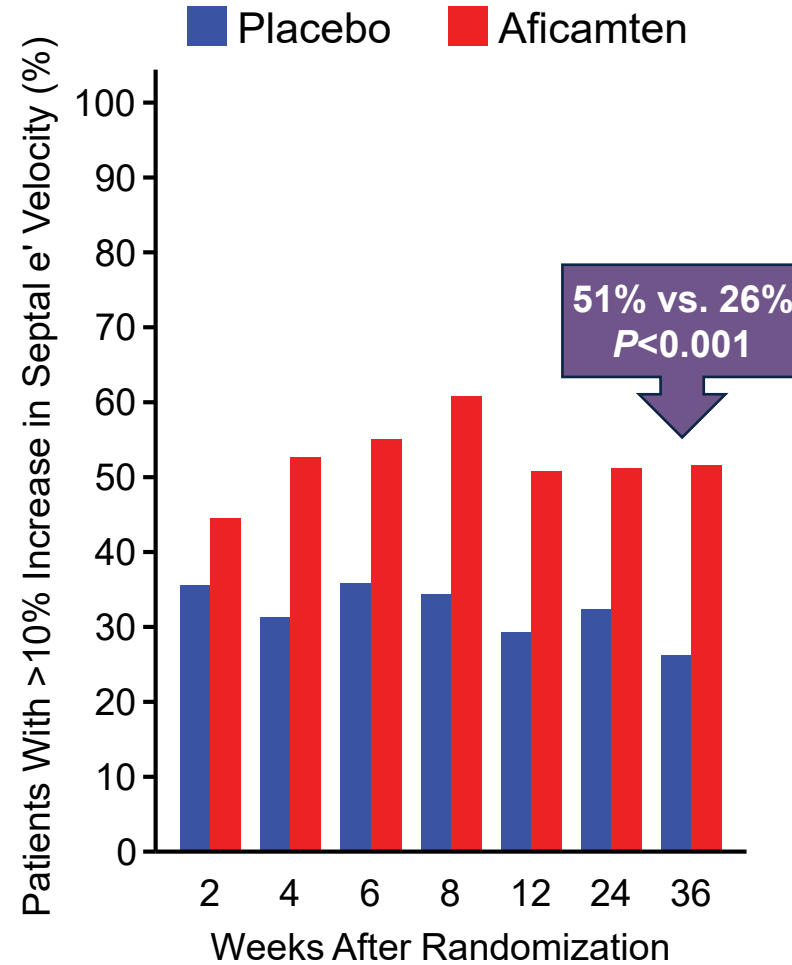
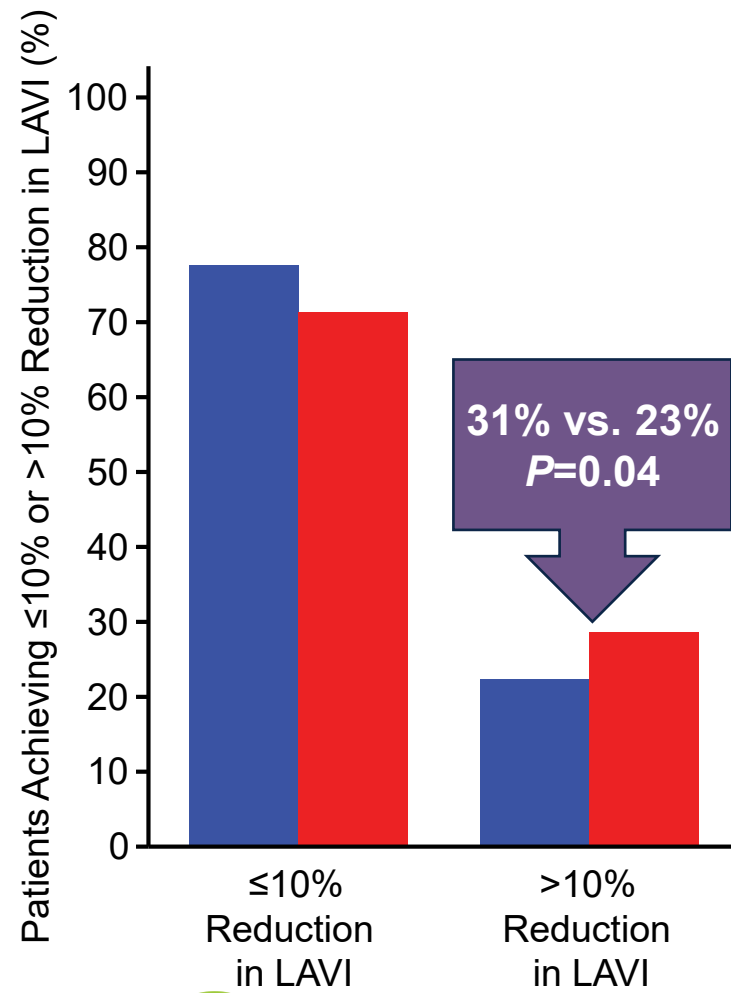
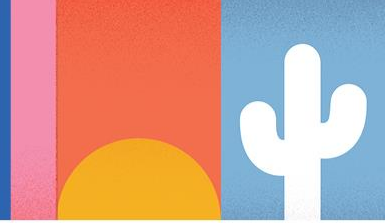


Change With Aficamten in Exercise Capacity by pVO₂ and Limiting Symptoms With NYHA Functional Class

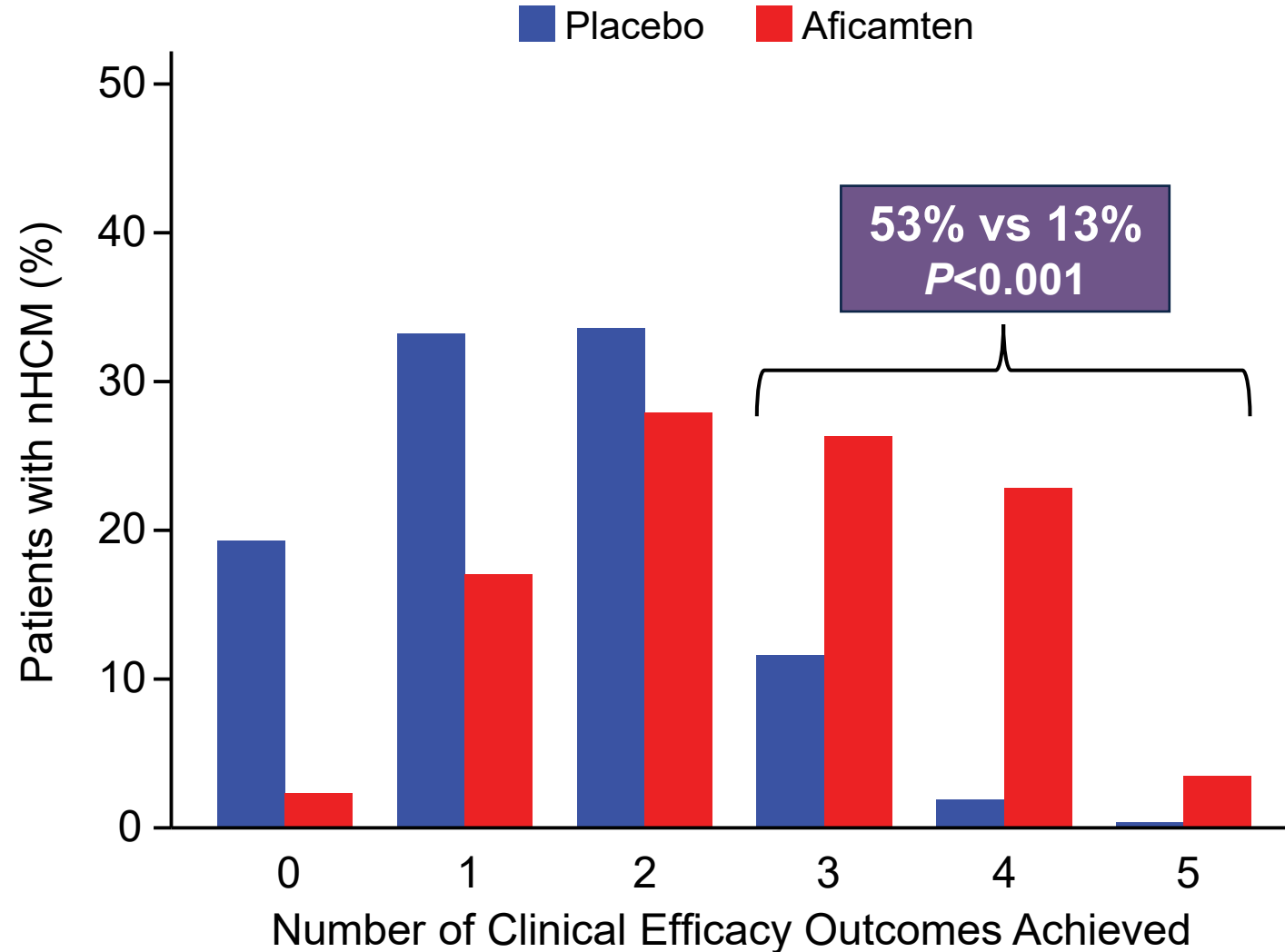
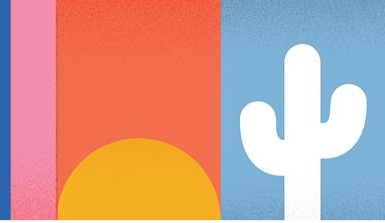


Outcome, n (%)	Placebo n=259 n (%)	Aficamten n=258 n (%)	Risk Difference vs Placebo (95% CI); <i>P</i> value
≥0.5 mL/kg/min increase in pVO ₂ and ≥1 NYHA class improvement	33(13)	54 (21)	8.1% (1.7%, 14.5%) <i>P</i> =0.013
≥1.0 mL/kg/min increase in pVO ₂ and ≥1 NYHA class improvement	26 (10)	44 (17)	7% (1.1%, 13%) <i>P</i> =0.019
≥1.5 mL/kg/min increase in pVO ₂ and no worsening of NYHA class	54 (21)	74 (29)	7.8% (0.4%, 15%) <i>P</i> =0.038

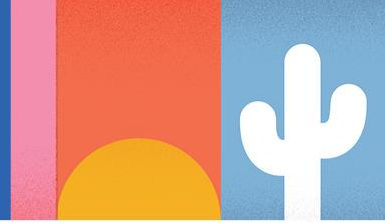
Clinical Response Measures From Baseline to Week 36 in Patients With nHCM



Proportion of Patients With nHCM Who Achieve Clinically Relevant Outcome on Aficamten vs Placebo

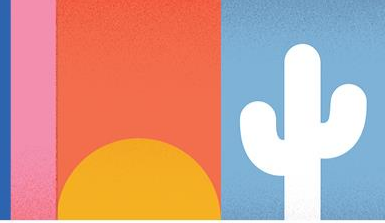


Impact of Treatment Effect Relative to Placebo



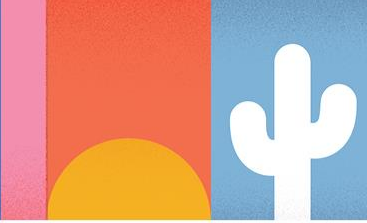
Outcome	Placebo n (%)	Aficamten n (%)	Risk Difference (95% CI)	NNT
Improvement in HF symptoms	136 (53)	182 (71)	18% (10, 27)	5.5
Increased Exercise Capacity	97 (37)	115 (45)	7% (-1.3, 16)	14.0
>10% Decrease in LAVI	60 (23)	80 (31)	7.8% (0.2, 15)	12.9
>10% Increase in septal e'	68 (26)	133 (51)	25% (17, 33)	4.0
≥50% Decrease in NT-proBNP	14 (5)	163 (63)	59% (52, 65)	1.7

Summary



- Over a relatively short treatment period, a majority (53%) of patients with nHCM treated with aficamten experienced a clinically meaningful improvement in ≥ 3 clinically relevant outcome measures, including:
 - Relief in limiting symptoms
 - Enhanced exercise capacity
 - Significant decrease in NT-proBNP
 - Improvement in diastolic function (decrease in LAVI and increase in septal e')
- Number needed to treat for aficamten ranged from 1.7 (NT-proBNP) to 14 (pVO₂ improvement) vs placebo
- These findings underscore the treatment effect of aficamten across a broad range of clinically relevant measures, including symptom burden and diastolic function, underscoring the benefit of aficamten in this largely underserved population of patients with symptomatic nHCM

Disclosures & Acknowledgments



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