

Aficamten for Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

Primary Results of the ACACIA-HCM Trial



Ahmad Masri, MD, MS¹, Caroline J. Coats, MD, PhD, Martin S. Maron, MD, Carolyn Y. Ho, MD;
on behalf of the ACACIA-HCM investigators

¹Oregon Health & Science University, Portland, Oregon, USA

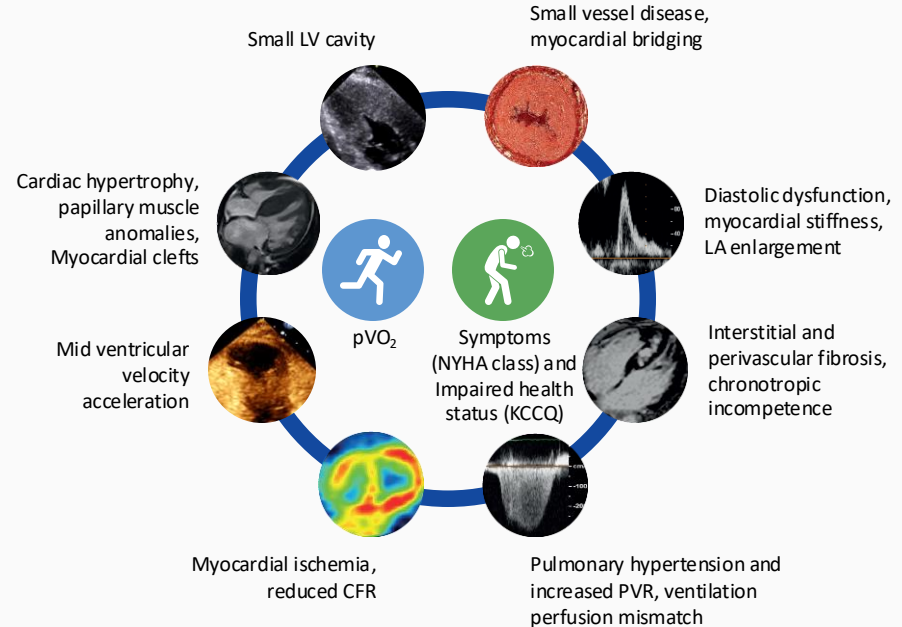
Co-authors: Ankit Bhatia, MD, Maria Luisa Peña Peña, MD, Mark V. Sherrid, MD, Estevao Lanna Figueiredo, MD, MSc, Michael Arad, MD, MSc, Roberto Barriaes-Villa, MD, PhD, Lubna Choudhury, MD, MRCPI, Brian L. Claggett, PhD, Caroline J. Coats, MD, PhD, Edileide de Barrios Correia, MD, Juan Pablo Costabel, MD, Perry M. Elliott, MBBS, MD, Jorge E. Silva Enciso, MD, Pablo Garcia-Pavia, MD, PhD, Junbo Ge, MD, Sheila M. Hegde, MD, MPH, Gregory D. Lewis, MD, Renato D. Lopes, MD, PhD, Matthew W. Martinez, MD, Mathew S. Maurer, MD, Zi Michael Miao, MS, Michelle Michels, MD, PhD, Sumeet S. Mitter, MD, MSc, Jesus E. Pino Moreno, MD, Iacopo Olivotto, MD, Anjali T. Owens, MD, Steen H. Poulsen, MD, Florian Rader, MD, Ethan J. Rowin, MD, P. Christian Schulze, MD, PhD, Robert Sepp, MD, PhD, Nikhil Sikand, MD, Scott D. Solomon, MD, John A. Spertus, MD, MPH, Charles Teale Sr., MPA, Xiaoyan Zhao, MD, Punag H. Divanji, MD, Stephen B. Heitner, MD, Daniel L. Jacoby, MD, Stuart Kupfer, MD, Fady I. Malik, MD, PhD, Joel Salazar-Mendiguchía, MD, PhD, Amy Wohltman, ME, Shu Zhuo, MS, Carolyn Y. Ho, MD, on behalf of the ACACIA-HCM Investigators

Disclosures

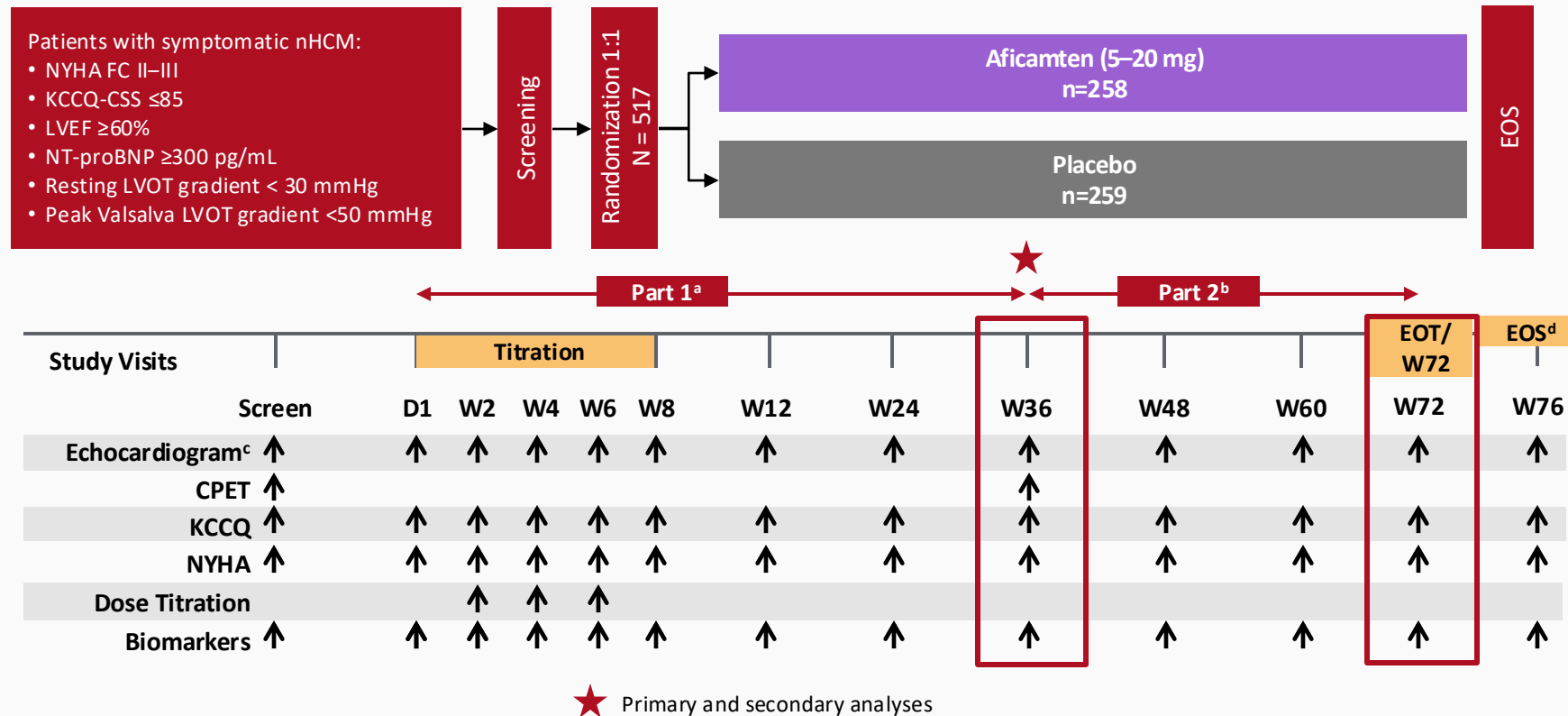
- **Ahmad Masri** has received research grants from Attralus, Cytokinetics and Janssen, and consulting fees from Cytokinetics, BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Akros, Edgewise, Rocket, Lexeo, Prothena, BioMarin, Intellia, Bayer, Imbria, Braveheart, AstraZeneca, Avidity, and Neurimmune.

Background

- Nonobstructive hypertrophic cardiomyopathy (nHCM) is a common heart disease associated with significant disease burden and no effective therapies.¹
- Patients with nHCM experience debilitating symptoms with exertion that limit their exercise capacity.²
- Aficamten is an allosteric, reversible cardiac myosin inhibitor approved in obstructive HCM.³ It has:
 - Favorable effects on diastolic function, a predominant pathophysiologic mechanism driving symptoms and decreased exercise capacity in nHCM.⁴⁻⁷
 - Favorable pharmacologic properties that allow for rapid titration, dose adjustment, and good tolerability.⁸



Methods: Study Design



Methods: Endpoints

- **Dual Primary Endpoints**

- Change from baseline to Week 36 in **KCCQ-CSS**.
- Change from baseline to Week 36 in **pVO₂ on CPET**.



Graphical multiplicity testing with equal alpha-split (0.025) for each

- **Secondary Efficacy Endpoints (hierarchical)**

- Changes from baseline to Week 36 in:
 - Proportion of participants with improvement of ≥ 1 NYHA functional class.
 - Composite Z-score of pVO₂ and ventilatory efficiency slope.
 - Proportional change in NT-proBNP concentration.
 - Left atrial volume index.^a
 - Time to first composite cardiovascular event.^b

- **Safety Outcomes**

- Safety endpoints included incidences of adverse events, LVEF <50% in association with clinical heart failure, and LVEF <40% leading to treatment interruption.

^a In patients without atrial fibrillation or flutter on baseline electrocardiogram.

^b Includes cardiovascular death, heart transplantation or left ventricular assist device, aborted sudden cardiac death, non-fatal stroke, heart failure hospitalization, or cardiac arrhythmia (atrial fibrillation or ventricular tachyarrhythmia requiring treatment or hospitalization).

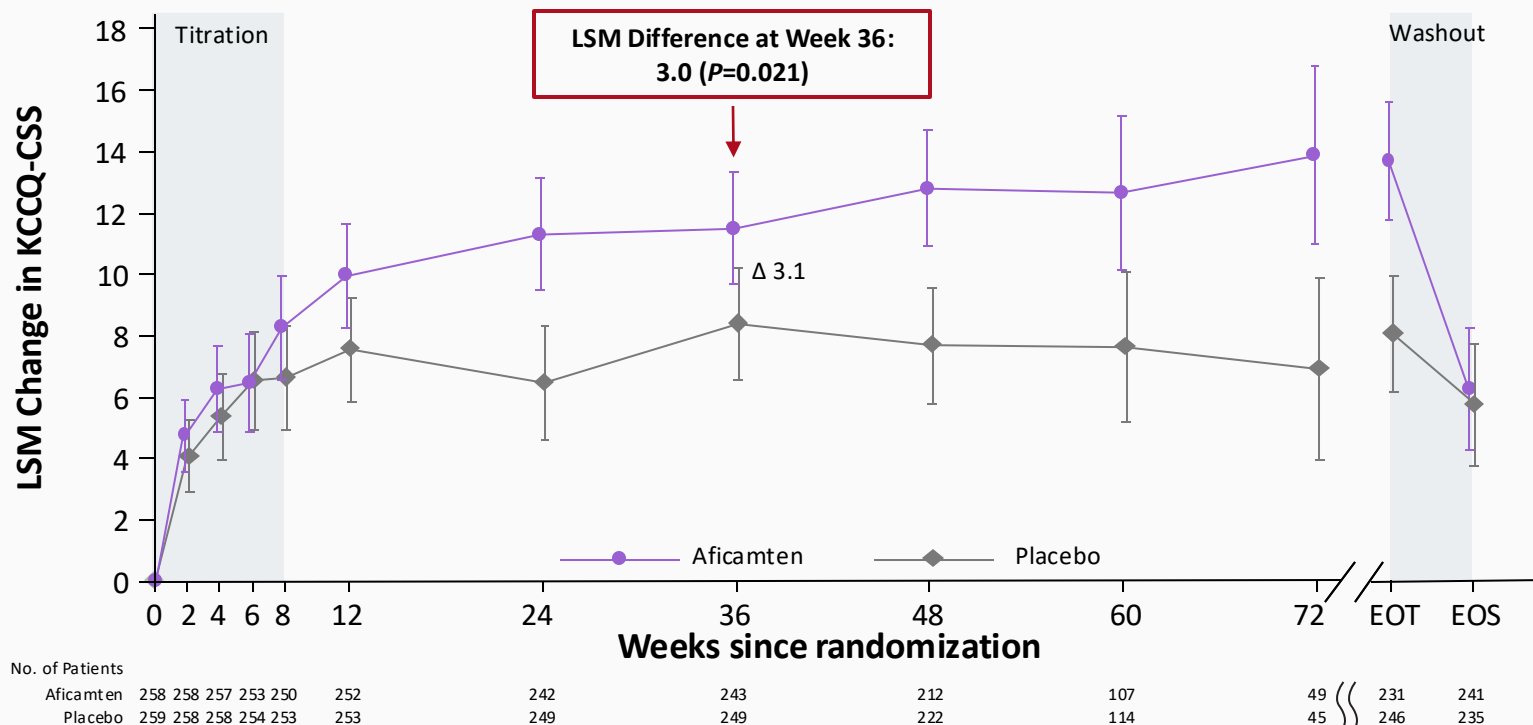
CPET, cardiopulmonary exercise test; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pVO₂, peak oxygen uptake.

Results: Baseline Characteristics

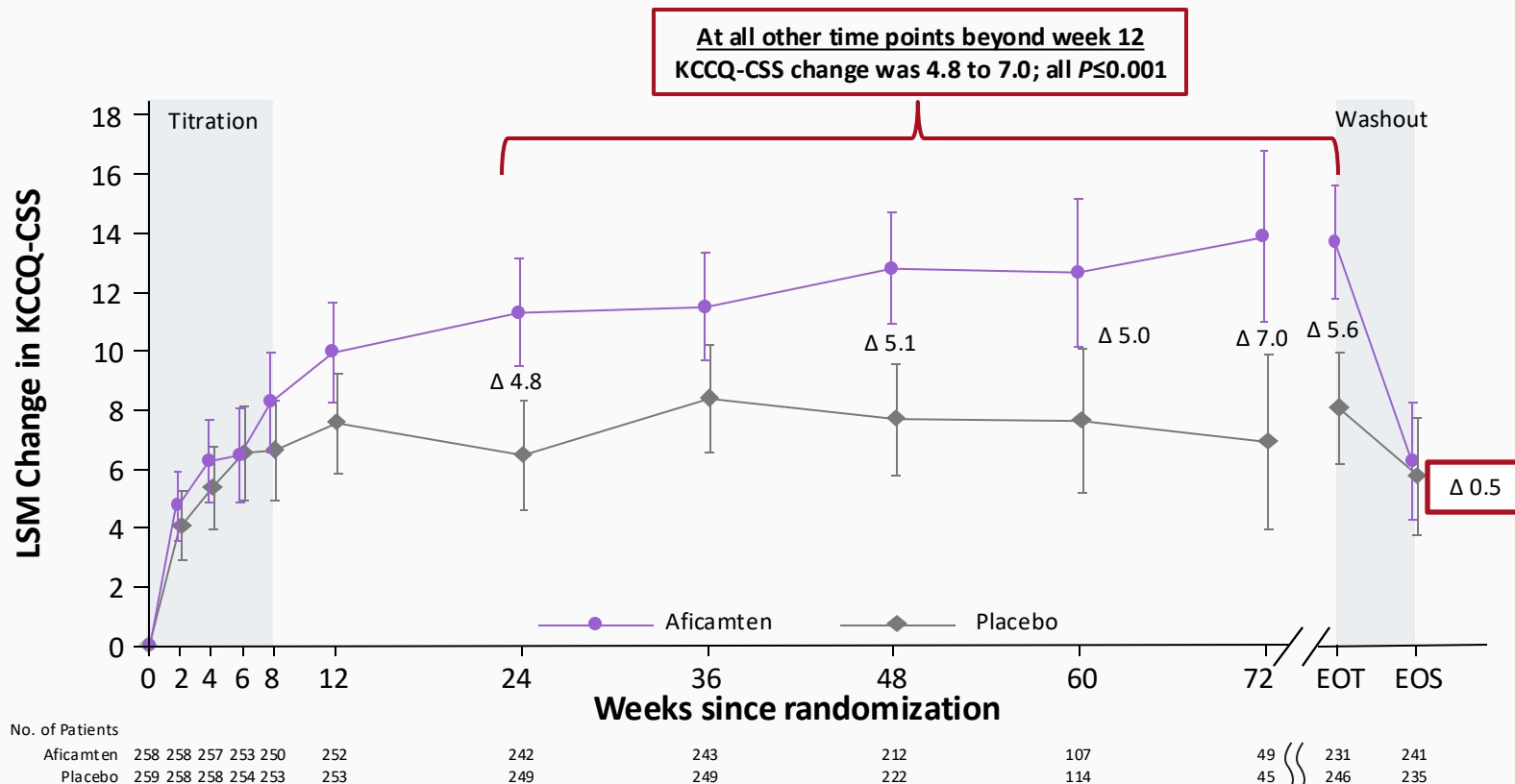
Characteristic	Aficamten (n=258)	Placebo (n=259)
Age, y	55.7 ± 16.2	54.5 ± 16.0
Female sex	140 (54.3)	137 (52.9)
Race or ethnic group ^a		
White	200 (77.5)	188 (72.6)
Asian	30 (11.6)	39 (15.1)
Black	17 (6.6)	16 (6.2)
Medical history		
Hypertension	101 (39.1)	101 (39.0)
Familial HCM ^b	173 (67.1%)	168 (64.9%)
Paroxysmal AF/AFL	78 (30.2)	68 (26.3)
Persistent or permanent AF	20 (7.8)	19 (7.3)
Intracavitary obstruction	22 (8.5)	26 (10.0)
Background HCM therapy		
Beta-blocker	203 (78.7)	197 (76.1)
Nondihydropyridine CCB	31 (12.0)	39 (15.1)
None	34 (13.2)	42 (16.2)

Characteristic	Aficamten (n=258)	Placebo (n=259)
Implantable cardioverter-defibrillator	107 (41.5)	105 (40.5)
KCCQ-CSS	66.3 ± 16.2	65.0 ± 15.4
NYHA class III	84 (32.6)	74 (28.6)
NT-proBNP, pg/mL	906 [508–1529]	893 [492–1609]
hs-cTnI, ng/L	30 [15–77]	28 [14–113]
CPET		
pVO ₂ , mL/kg/min	18.0 ± 5.3	18.0 ± 5.1
Predicted pVO ₂ , %	55.3 ± 13.1	54.9 ± 12.7
Peak RER	1.2 ± 0.1	1.2 ± 0.1
VE/VCO ₂	35.10 (7.9)	34.29 (6.7)
Echocardiographic parameters		
Valsalva LVOT-G, mmHg	11.8 ± 8.8	11.4 ± 8.5
Resting LVOT-G, mmHg	9.1 ± 6.1	8.2 ± 4.6
LVEF, %	67.9 ± 4.0	68.4 ± 3.4
Maximal LV wall thickness, mm	22.3 ± 5.2	23.1 ± 5.7
LAVI, mL/m ²	36.8 ± 10.9	37.5 ± 11.9

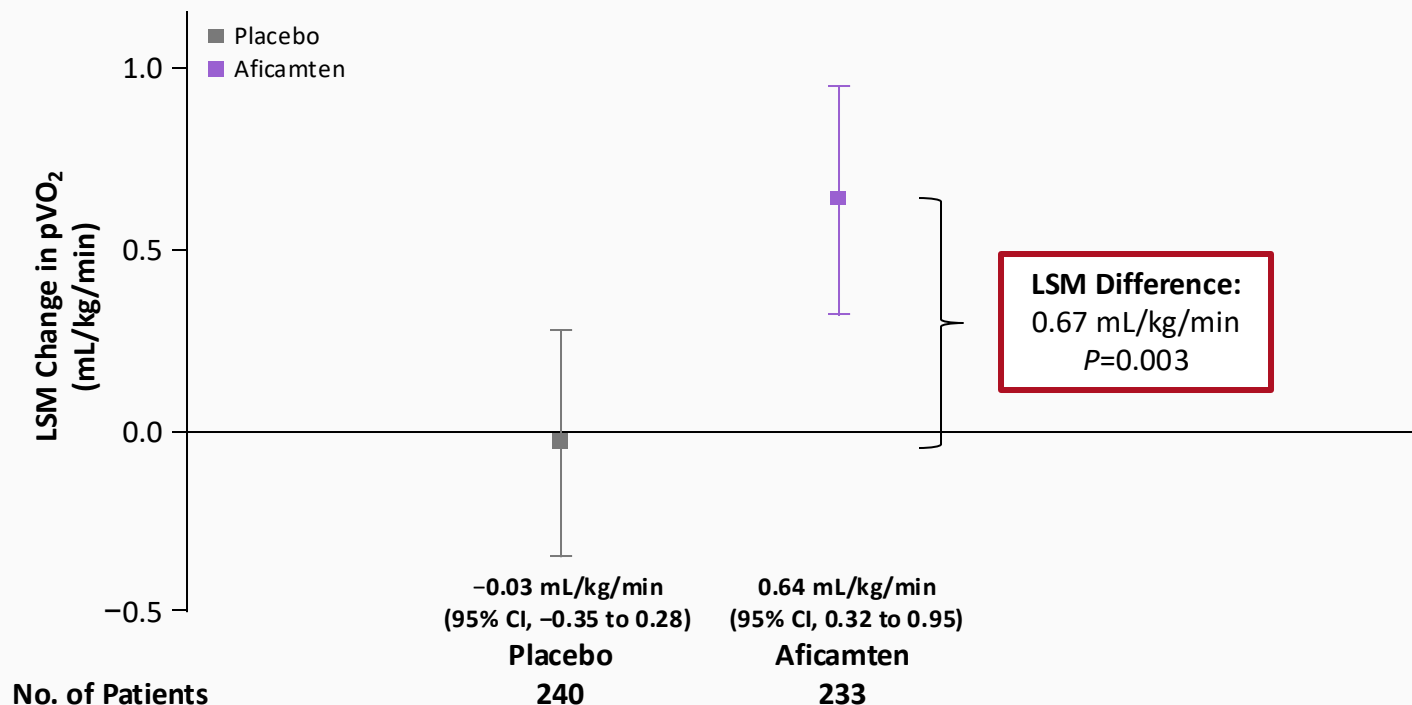
Results: KCCQ-CSS (Dual Primary Endpoint at Week 36)



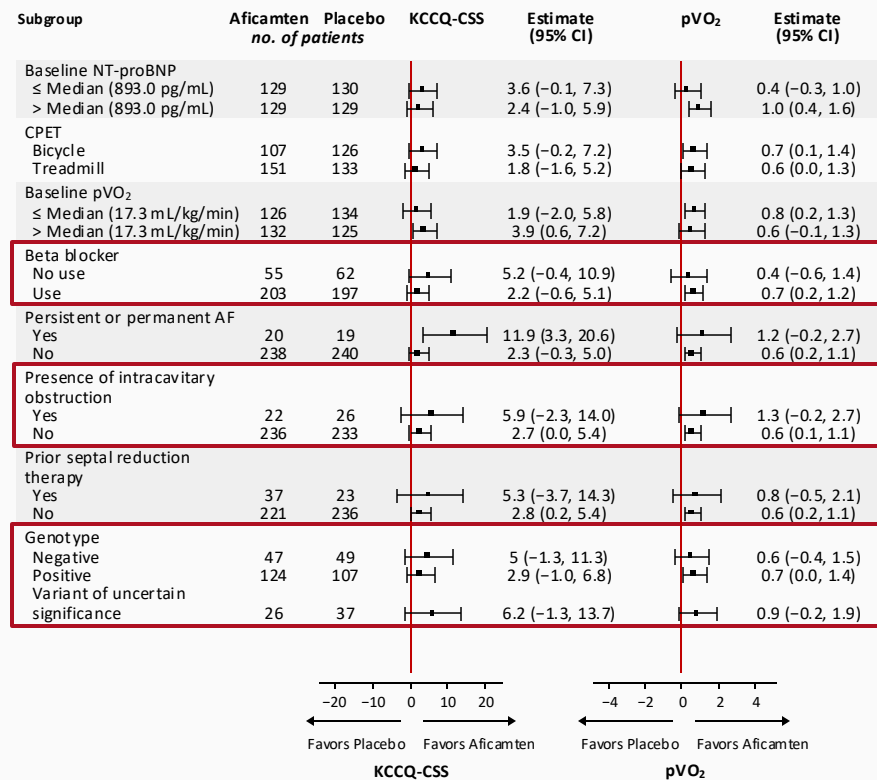
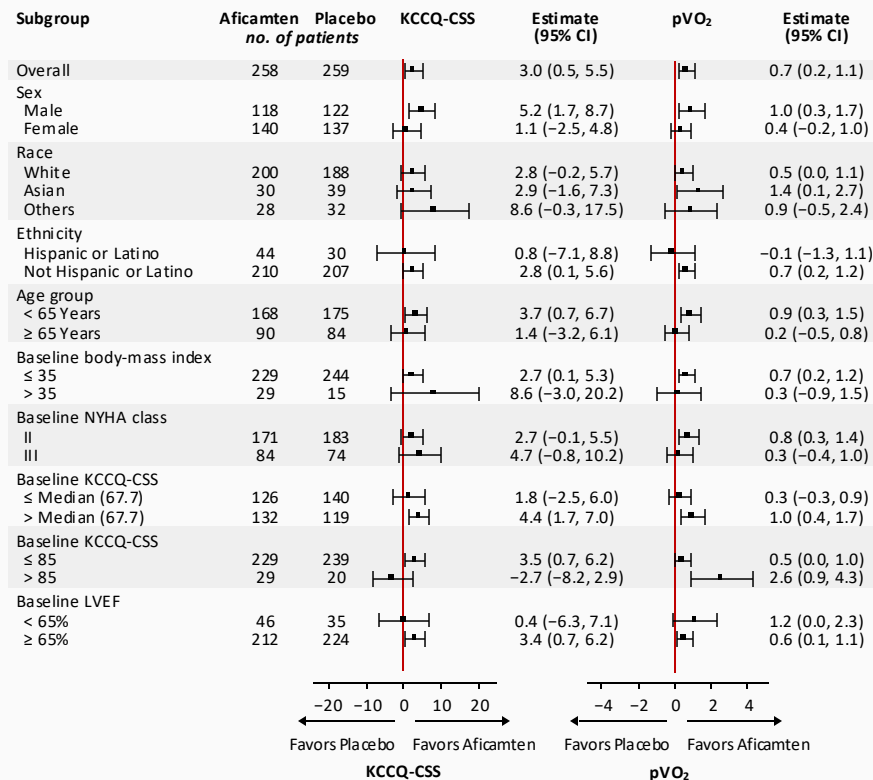
Results: KCCQ-CSS (Dual Primary Endpoint at Week 36)



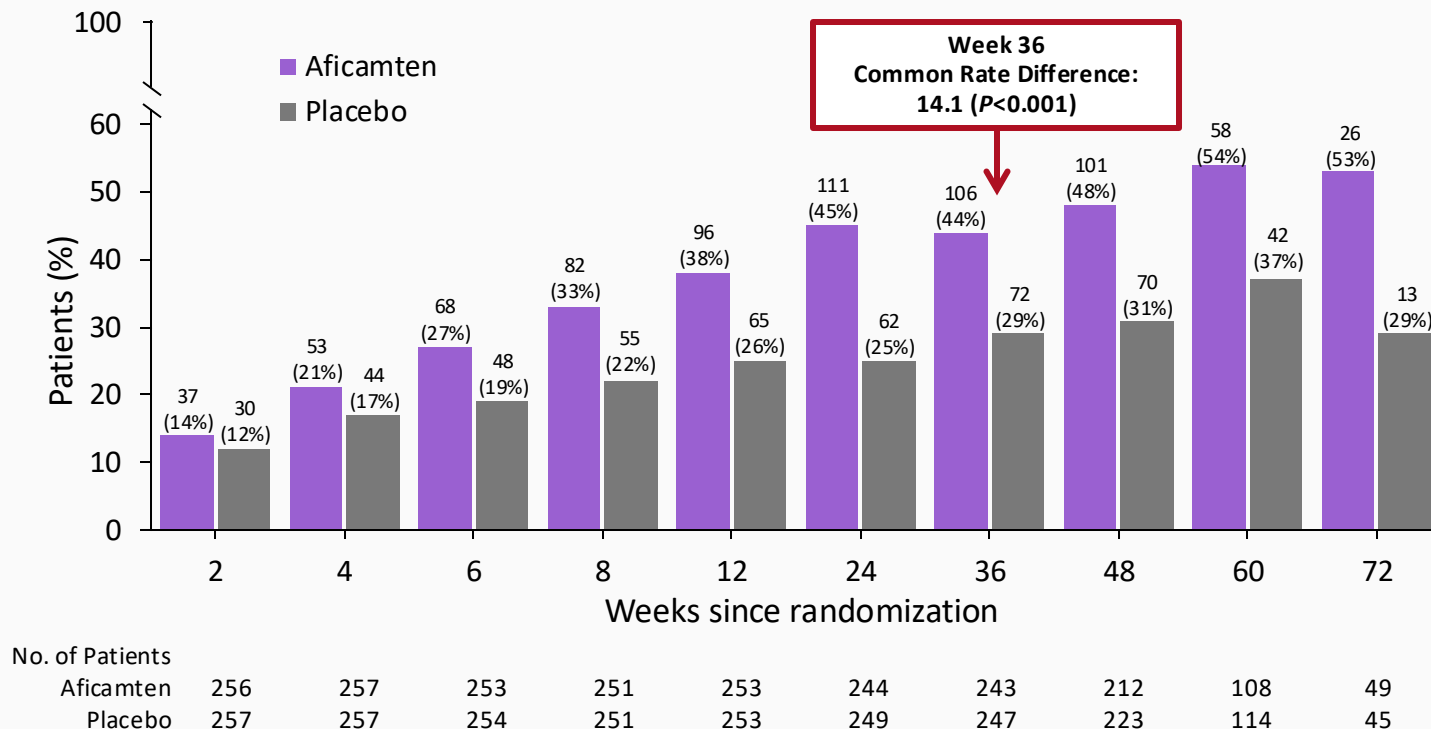
Results: Change in pVO₂ (Dual Primary Endpoint at Week 36)



Consistent Results for Both Endpoints Across Prespecified Subgroups

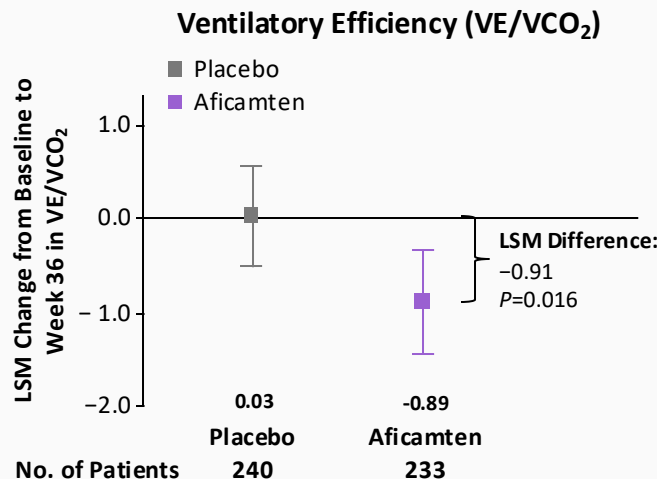
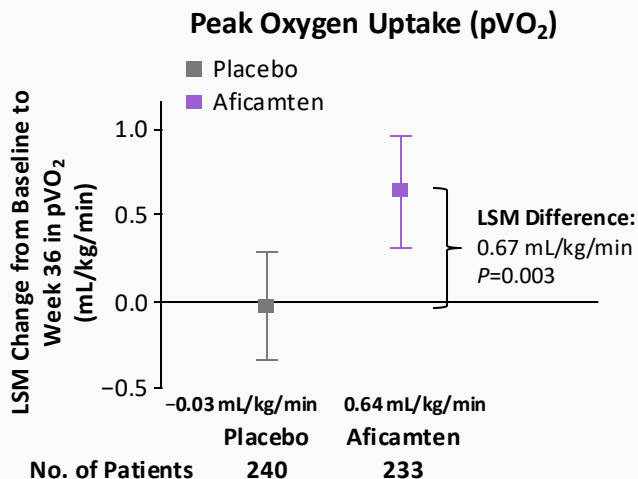


Results: Improvement in ≥ 1 NYHA Functional Class



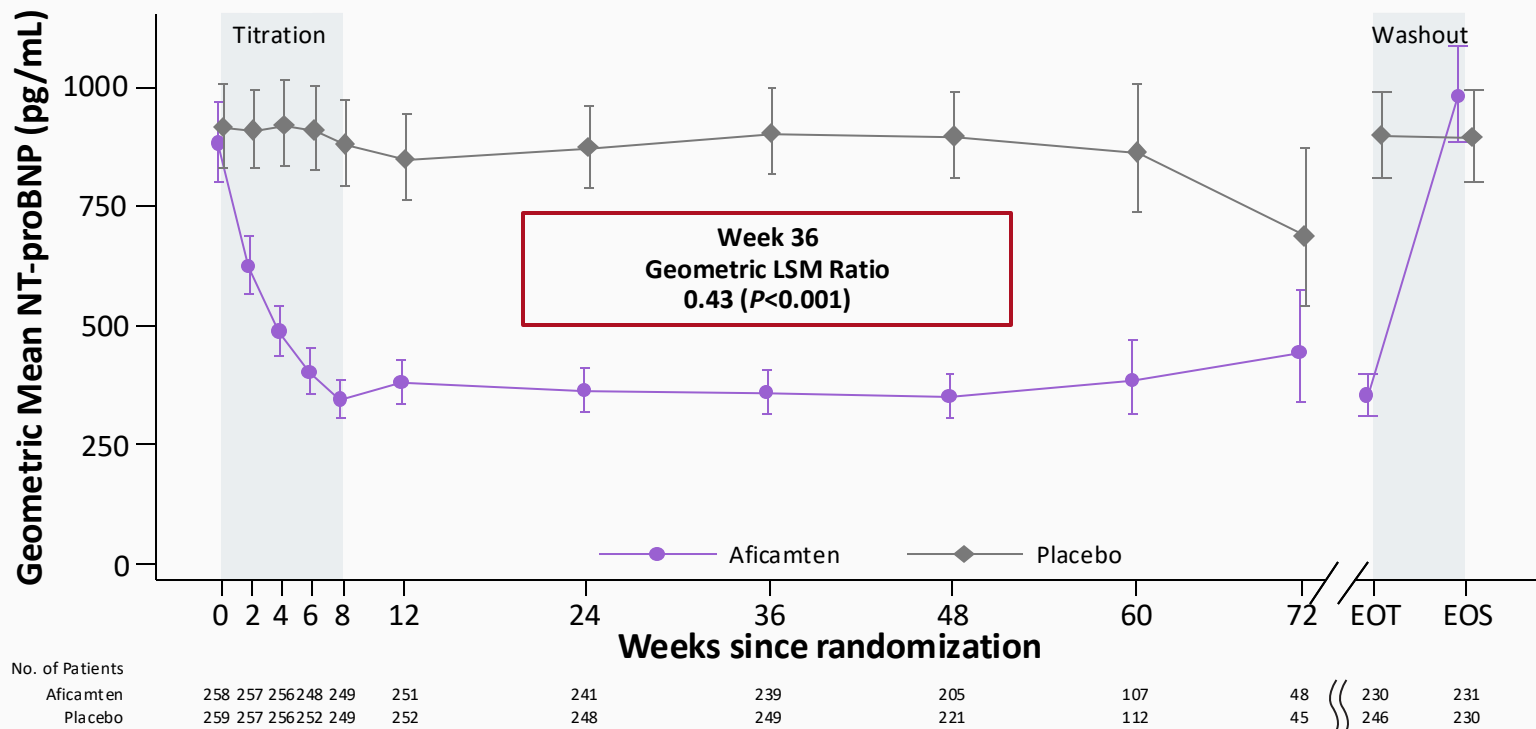
Results: Improvement in Comprehensive Exercise Performance

CPET Z-Score



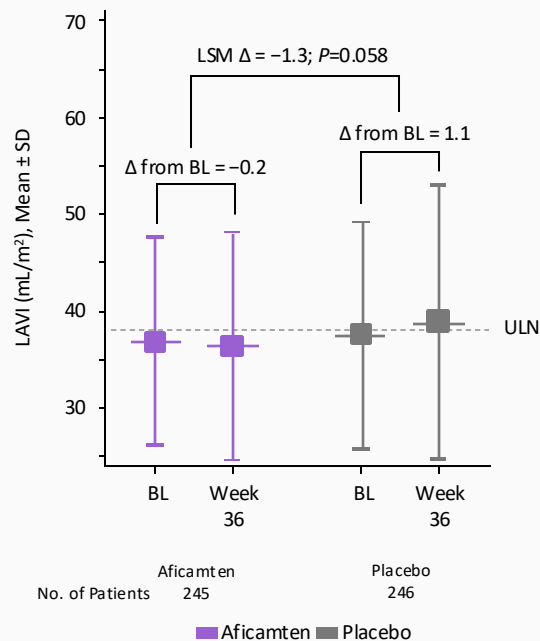
Aficamten: 0.05 (95% CI, -0.01 to 0.11) vs. Placebo: -0.09 (95% CI, -0.14 to -0.04)
Mean difference 0.14 (95% CI, 0.07 to 0.22), $P<0.001$

Results: NT-proBNP Concentration Over Time

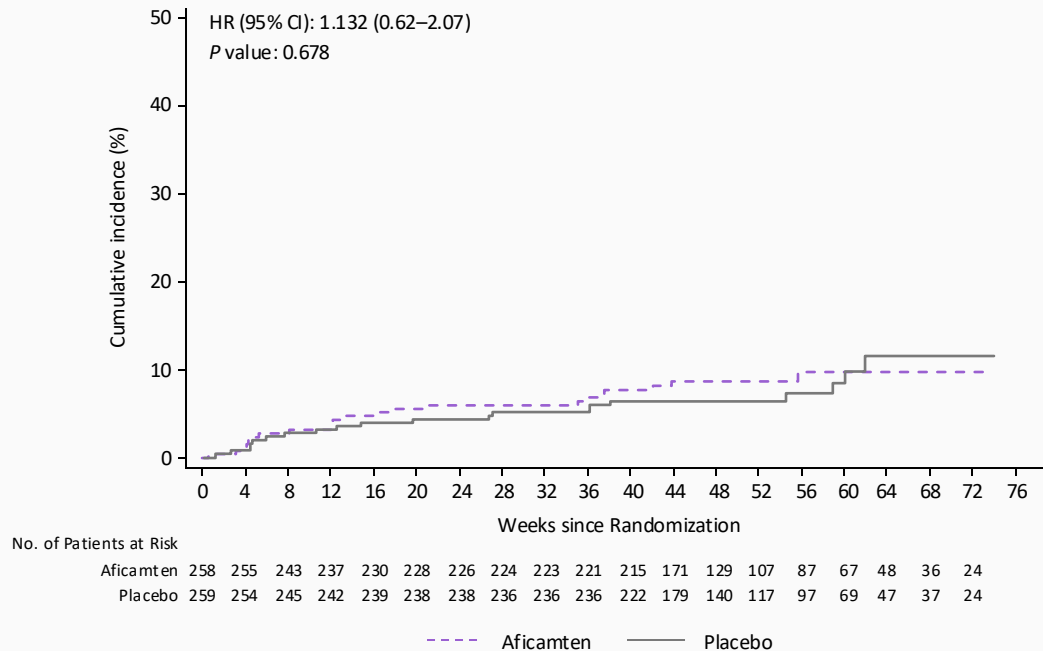


Results: LAVI and Time to First Cardiovascular Event

Change from BL at Week 36 in LAVI

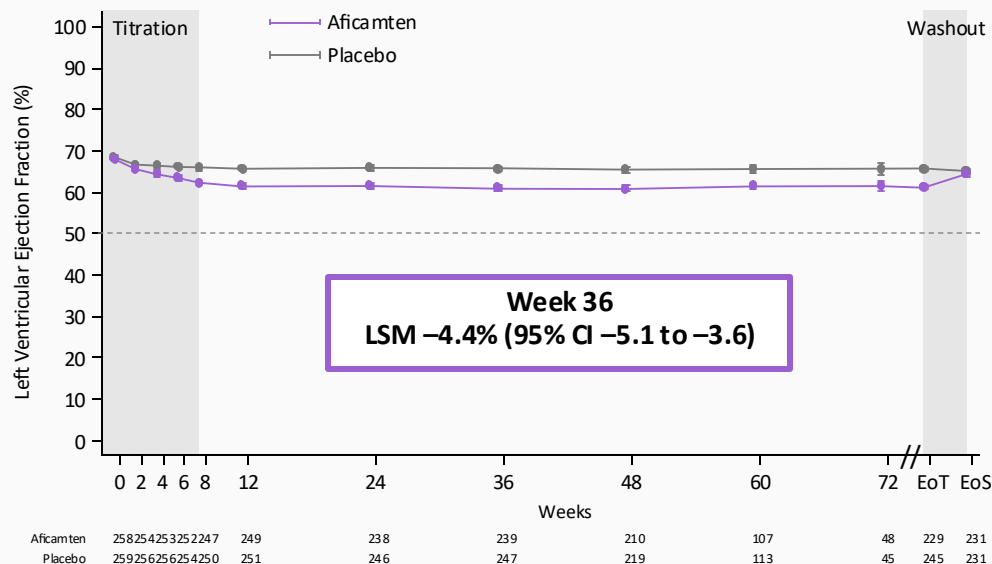


Time to First Composite Cardiovascular Event^a



Results: Safety Outcomes

- Aficamten was generally well-tolerated without new safety signals
 - Aficamten was titrated to maximum tolerated doses as guided by LVEF
 - 80.7% of patients were on 15-20 mg by the end of the titration period, and 79.4% of patients were on 15-20 mg by the end of the treatment period.
- At week 36, the LVEF LSM difference between aficamten and placebo was -4.4% (95% CI, -5.1 to -3.6).
 - Only 3% of the patients who received aficamten had treatment interruption due to reduced left ventricular ejection fraction



Results: Safety Outcomes

Event, n (%)	Aficamten (n=258)	Placebo (n=259)
Any AE	207 (80.2)	217 (84.1)
Any nonfatal AE that led to treatment discontinuation	18 (7.0)	5 (1.9)
Any nonfatal AE that led to early study discontinuation	9 (3.5)	2 (0.8)
Any SAE	52 (20.2)	38 (14.7)
Death	0 (0)	3 (1.2)
Heart Failure	12 (4.7)	3 (1.2)
New AF	4 (1.6)	3 (1.2)
Incidence of LVEF <50%	27 (10.5)	2 (0.8)
Incidence of LVEF <50% with any serious cardiac failure AE ^a	2 (0.8)	0
Incidence of LVEF <40%	7 (2.7)	0 (0)

All heart failure events in aficamten treated patients occurred during titration/prior to Week 12 and were generally responsive to a short course of diuretic therapy.

Of the 27 LVEF <50% events, 21 completed treatment while receiving the same or lower doses of aficamten.

Global Efficacy of Aficamten in Nonobstructive Hypertrophic Cardiomyopathy

A Pre-specified Sub-analysis

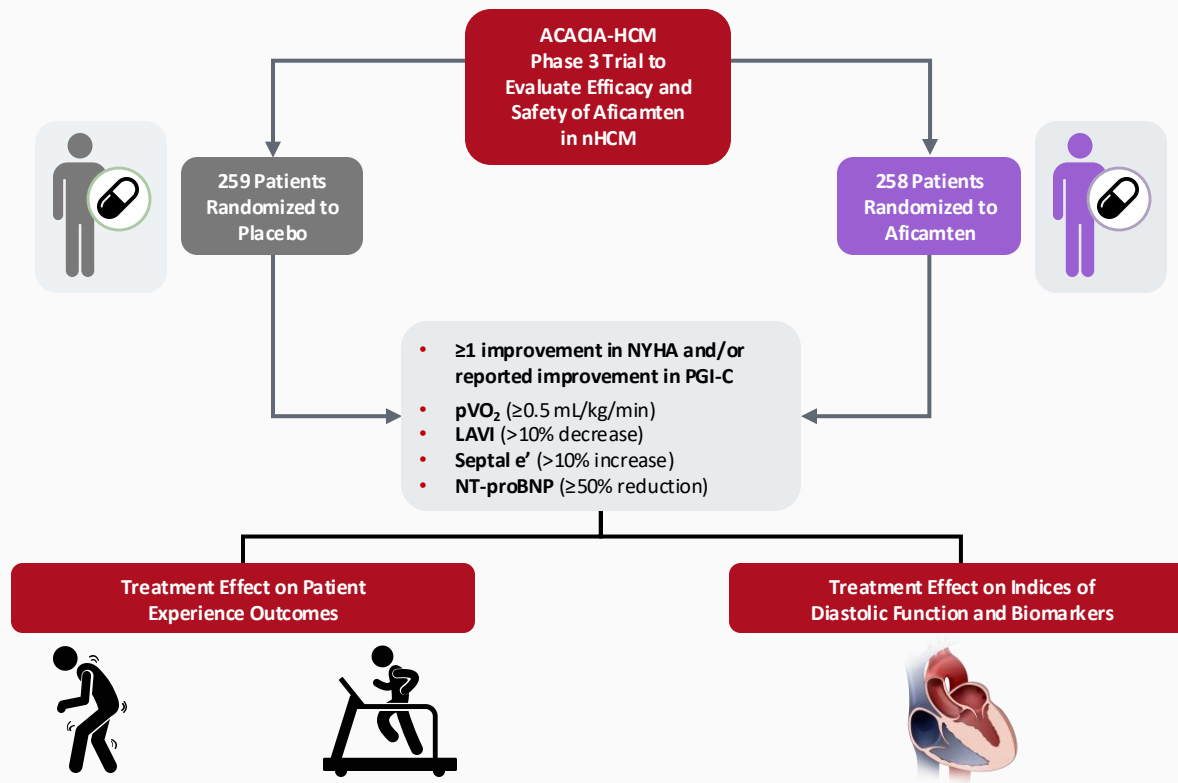


Ahmad Masri, MD, MS¹, on behalf of Martin S. Maron, MD² and the ACACIA-HCM Investigators

¹Oregon Health & Science University, Portland, Oregon, USA

²Lahey Hospital and Medical Center, Burlington, Massachusetts, USA

METHODS

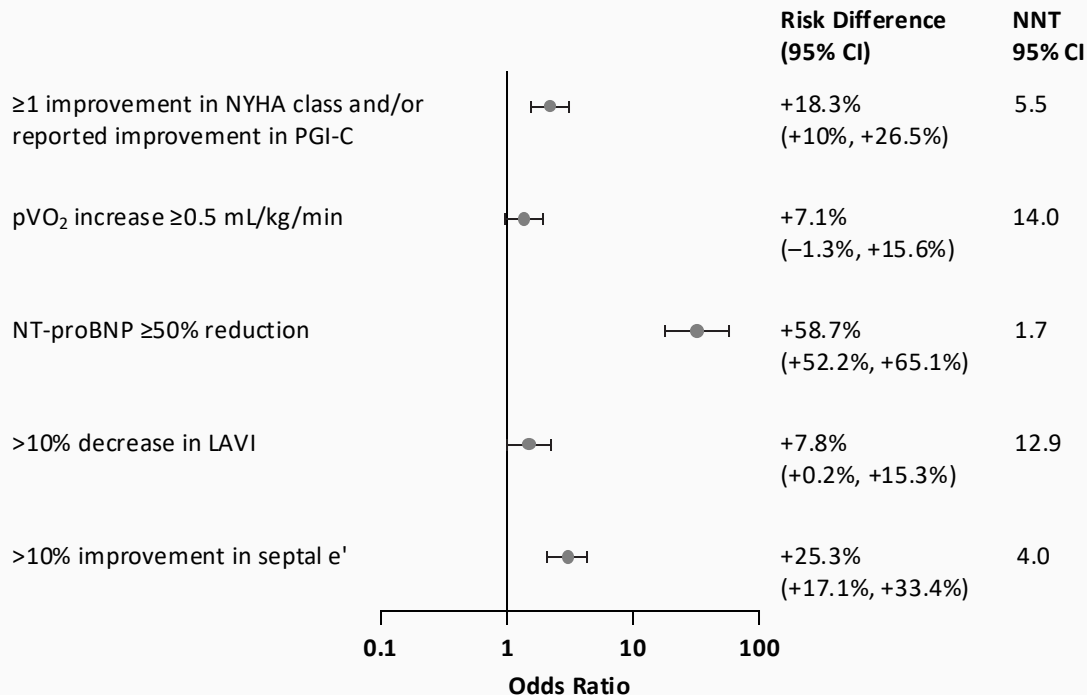


Patient Global Impression of Change (PGI-C)

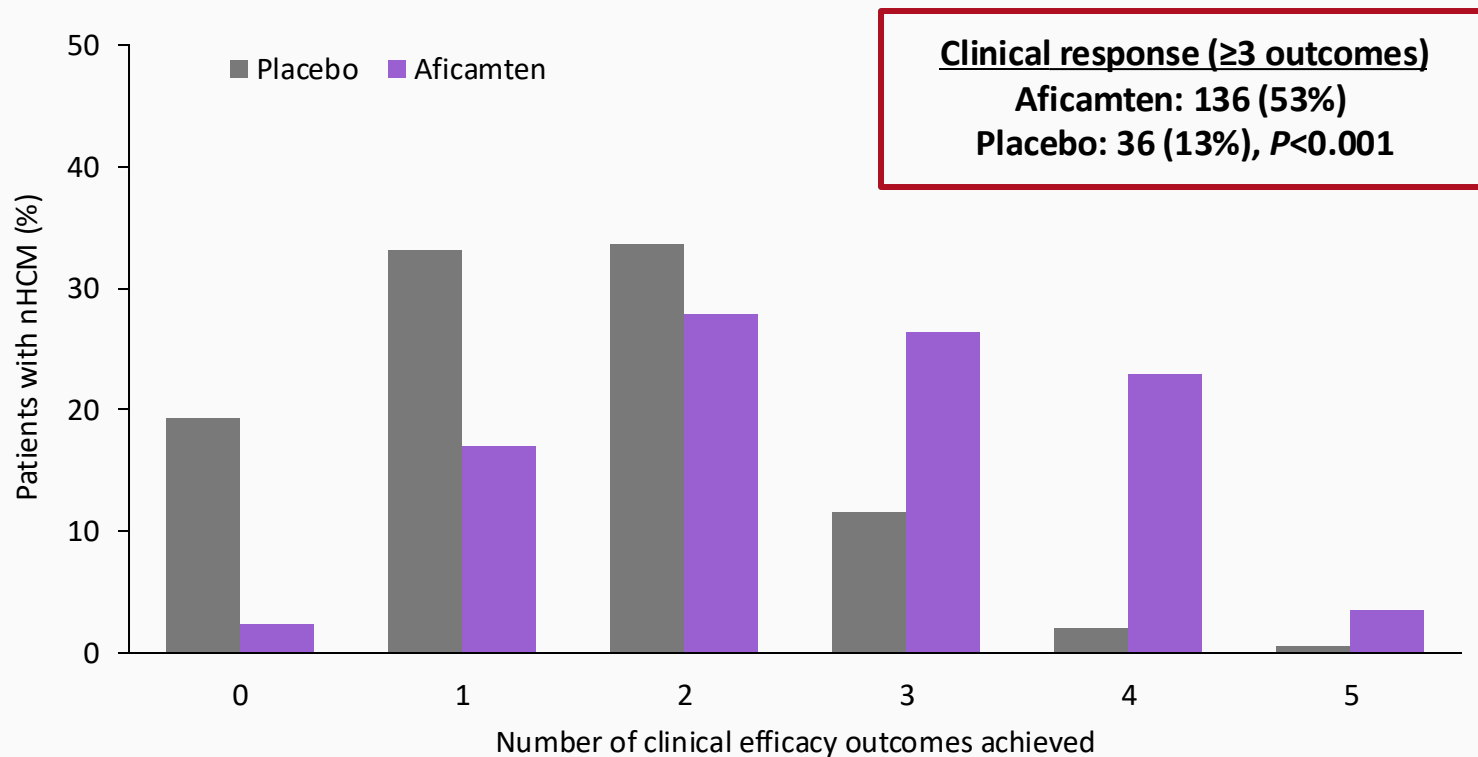
Please choose the response below that best describes the overall change in your symptoms and overall health since you started taking the study medication.

- ☐ Very much better
- ☐ Moderately Better
- ☐ A Little Better
- ☐ No Change
- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Very Much Worse

Results: Effect of Aficamten vs Placebo on Clinical Efficacy Outcomes



Global Efficacy across Five Domains at Week 36



Conclusions

- Aficamten improved exercise capacity, patient-reported health status, and symptoms, as compared with placebo in patients with symptomatic nHCM.
- Over 36 weeks of treatment, aficamten yielded statistically significant improvements in efficacy as compared with placebo:
 - Dual primary endpoints (KCCQ-CSS and pVO_2).
 - Three of five secondary endpoints (NYHA class, exercise performance [Z-score], and NT-proBNP).
- Aficamten was generally well-tolerated, and the majority of reductions of LVEF < 50% were managed by simple down titration.
- In a prespecified responder analysis, aficamten positively affected a wide range of relevant clinical endpoints.
- These findings show that aficamten is an effective treatment for patients with nHCM.
- The 5-year ongoing FOREST-HCM trial will provide further data on the longer-term efficacy and safety of aficamten in nHCM, where >80% of eligible participants from ACACIA-HCM are currently enrolled.

Simultaneous Publications in *New England Journal of Medicine* and in *Circulation*



The NEW ENGLAND
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ORIGINAL ARTICLE

Aficamten for Symptomatic Nonobstructive Hypertrophic Cardiomyopathy

A. Masri,¹ M.S. Maron,² A. Bhatia,³ M.L. Peña-Peña,⁴ M.V. Sherrid,⁵
E.L. Figueiredo,⁶ M. Arad,^{7,8} R. Barriales-Villa,⁹ L. Choudhury,¹⁰ B.L. Claggett,¹¹
C.J. Coats,¹² E.B. Correia,¹³ J.P. Costabel,¹⁴ P.M. Elliott,^{15,16} J.E. Silva Enciso,¹⁷
P. Garcia-Pavia,^{18,19} J. Ge,²⁰ S.M. Hegde,^{21,22} G.D. Lewis,²³ R.D. Lopes,²⁴
M.W. Martinez,²⁵ M.S. Maurer,²⁶ Z.M. Miao,¹¹ M. Michels,²⁷ S.S. Mitter,²⁸
J.E. Pino Moreno,²⁹ I. Olivetto,³⁰ A.T. Owens,³¹ S.H. Poulsen,³² F. Rader,³³
E.J. Rowin,² P.C. Schulze,³⁴ R. Sepp,³⁵ N. Sikand,³⁶ S.D. Solomon,¹¹ J.A. Spertus,^{37,38}
C. Teale, Sr.,³⁹ X. Zhao,⁴⁰ P.H. Divanji,⁴¹ S.B. Heitner,⁴² D.L. Jacoby,⁴³ S. Kupfer,⁴⁴
F.I. Malik,⁴⁵ J. Salazar-Mendiguchia,⁴⁶ A. Wohltman,⁴⁴ S. Zhuo,⁴⁴ and C.Y. Ho,⁴¹
for the ACACIA-HCM Investigators⁴⁸



Circulation

Global Efficacy of Aficamten in Nonobstructive Hypertrophic Cardiomyopathy: Results from ACACIA-HCM

Martin S. Maron, MD; Ahmad Masri, MD, MS; Ankit Bhatia, MD; Maria Luisa Peña Peña, MD; Mark V. Sherrid, MD; Estevo Lanna Figueiredo, MD, MSc; Michael Arad, MD, MSc; Lubna Choudhury, MD, MRCPI; Brian L. Claggett, PhD; Caroline J. Coats, MD, PhD; Edleide de Barros Correia, MD; Juan Pablo Costabel, MD; Perry M. Elliott, MBBS, MD; Jorge E. Silva Enciso, MD; Junbo Ge, MD; Carolyn Y. Ho, MD; Ian Kulac, MS; Gregory D. Lewis, MD; Matthew W. Martinez, MD; Mathew S. Maurer, MD; Michelle Michels, MD, PhD; Sumeet S. Mitter, MD, MSc; Jesus E. Pino Moreno; Iacopo Olivetto, MD; Anjali T. Owens, MD; Steen H. Poulsen, MD; Florian Rader, MD; Ethan J. Rowin, MD; P. Christian Schulze, MD, PhD; Robert Sepp, MD, PhD; Nikhil Sikand, MD; Scott D. Solomon, MD; John A. Spertus, MD, MPH; Xiaoyan Zhao, MD; Punag H. Divanji, MD; Stephen B. Heitner, MD; Daniel L. Jacoby, MD; Stuart Kupfer, MD; Fady I. Malik, MD, PhD; Joel Salazar-Mendiguchia, MD, PhD; Amy Wohltman, MD; Shu Zhuo, MS; Roberto Barriales-Villa, MD, PhD on behalf of the ACACIA-HCM Investigators



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