



ASM 2026

HFSA ANNUAL SCIENTIFIC MEETING

**Where Heart Failure Teams Gather
October 9-12, 2026 | Phoenix, Arizona**

Dose Titration and Safety Profile of Aficamten in Nonobstructive Hypertrophic Cardiomyopathy: Findings from ACACIA-HCM

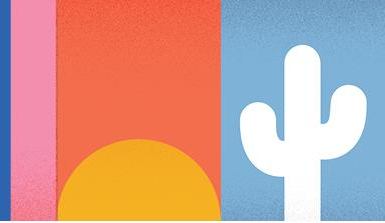
Ahmad Masri, MD, MS, on behalf of the ACACIA-HCM Investigators

Oregon Health and Science University, Portland, OR, USA

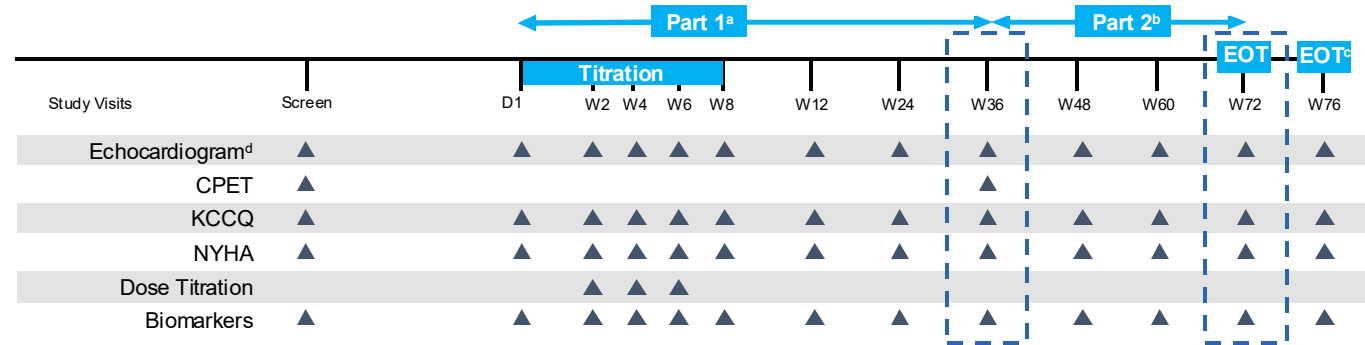
Co-authors: Caroline J. Coats, MD, PhD, Ankit Bhatia, MD, Maria Luisa Peña Peña, MD, Mark V. Sherrid, MD, Estevao Lanna Figueiredo, MD, MSc, Michael Arad, MD, MSc, Roberto Barriaes-Villa, MD, PhD, Lubna Choudhury, MD, MRCPI, Brian L. Claggett, PhD, Edileide de Barros Correia, MD, Juan Pablo Costabel, MD, Perry M. Elliott, MBBS, MD, Jorge E. Silva Enciso, MD, Junbo Ge, MD, Sheila M. Hegde, MD, MPH, Carolyn Y. Ho, MD, Gregory D. Lewis, MD, Martin S. Maron, MD, Matthew W. Martinez, MD, Mathew S. Maurer, MD, Zi Michael Miao, 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, 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, on behalf of the ACACIA-HCM Investigators



ACACIA-HCM: Dosing Strategy



- Treatment was titrated through an automated algorithm to the **maximum tolerated dose** guided solely by LVEF
- This dosing approach contrasts with oHCM where trials target the **minimum effective dose** needed to relieve LVOTO.
- Rationale for this approach is to optimize drug effect on enhancing diastolic function whilst maintaining LVEF.



^a Part 1: All patients followed until W36.

^b Part 2: When ≥200 patients reach 52 weeks of treatment, all remaining active study patients who have completed W36 will be eligible for an EOT visit followed by an EOS visit.

^c To occur ≥4 weeks after the last dose of investigational product.

^d Site-read focused echocardiogram for titration visit (sole criterion). Aficamten dose range 5–20 mg.

5 mg → 10 mg → 15 mg → 20 mg (by Week 8)

Patients with LVEF <40% have aficamten dosing temporarily interrupted.

Biplane LVEF <50%

Dose reduction

No change

Biplane LVEF ≥50% to <60%

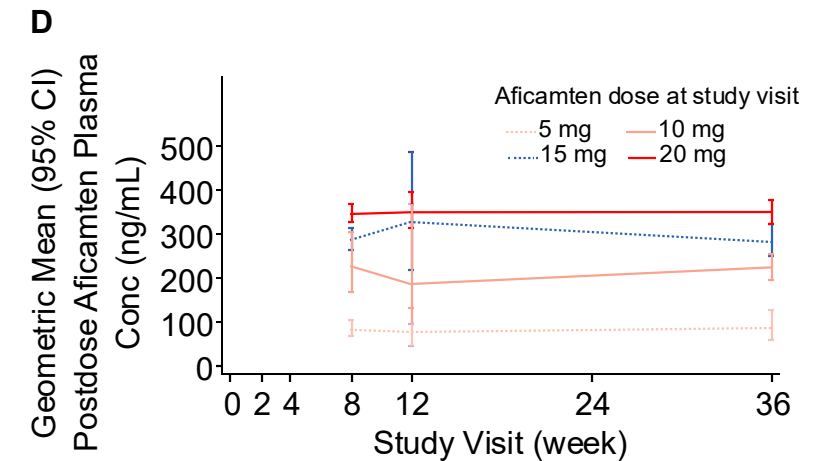
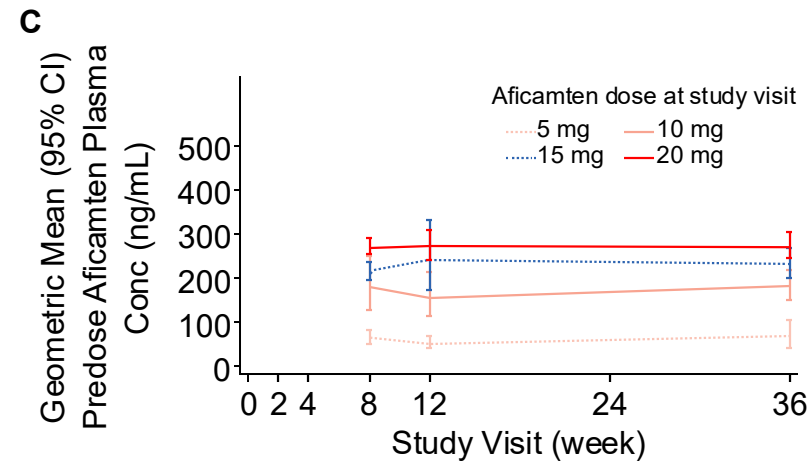
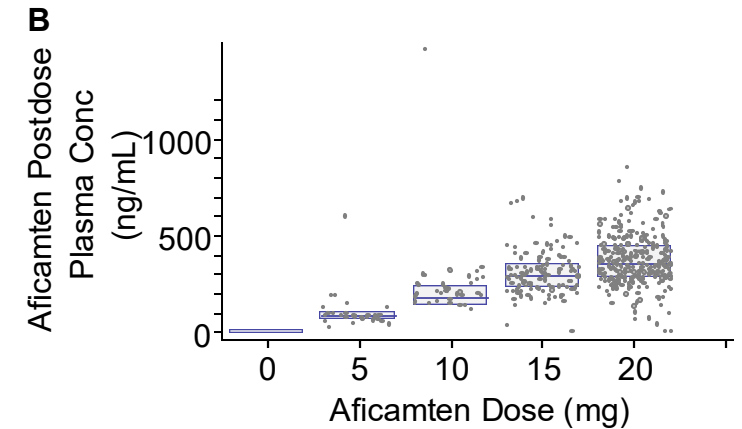
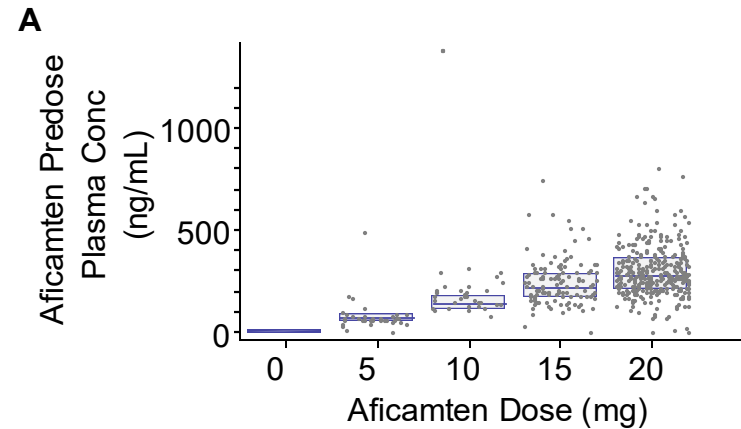
Dose increase

Biplane LVEF ≥60%

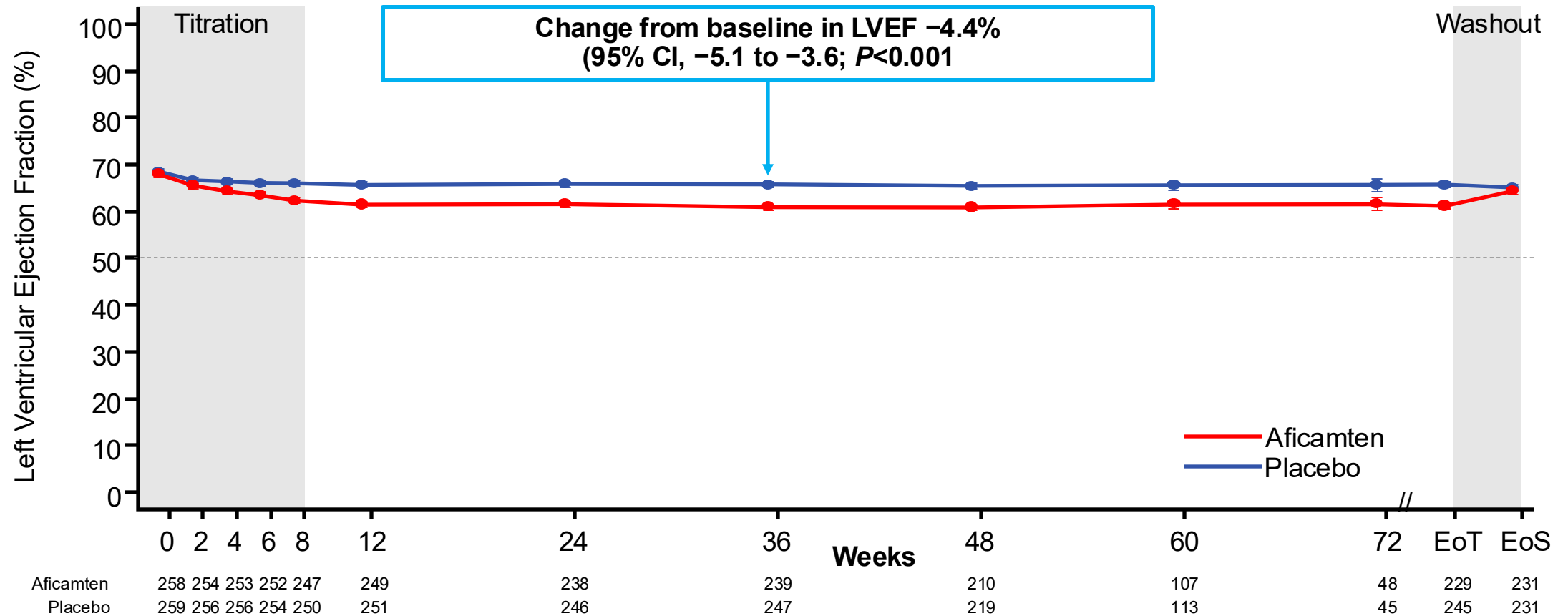
Doses Achieved, Plasma Concentration and Impact on LVEF

- 80.7% of patients were on 15-20 mg by the end of the titration period.
- At Week 8, LVEF decreased -1.1% (95% CI, -1.3 to -0.8) per 100 ng/mL aficamten exposure and remained stable.
- Aficamten had a low peak-to-trough ratio of 1.3.

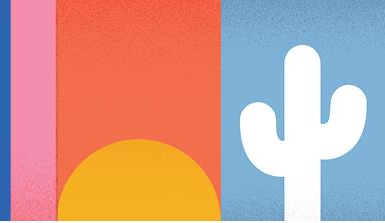
Plasma concentration increased proportional to dose, and remained stable from Weeks 8 to 36



Longitudinal Change in Mean LVEF



Characteristics of Patients Experiencing LVEF <50%



Variable*	No LVEF <50% n=488	Any LVEF <50% n=29 ^a	P Value
Age, y	54.8 ± 16.2	58.8 ± 13.0	0.20
Female Sex	257 (52.7)	20 (69.0)	0.09
BMI, kg/m ²	28.0 ± 4.8	28.6 ± 4.3	0.49
Permanent AF	30 (6.1)	5 (17.2)	0.021
Paroxysmal AF	137 (28.1)	9 (31.0)	0.73
NT-proBNP, pg/mL	888 [498–1554]	1131 [637–1773]	0.43
hs-Troponin I, ng/L	28 [14, 86]	31 [15, 183]	0.44
KCCQ-CSS	65.9 ± 15.7	62.6 ± 18.2	0.28
pVO ₂ , mL/kg/min	18.1 ± 5.2	16.2 ± 3.9	0.05
Baseline LVEF, %	68.3 ± 3.4	65.0 ± 6.5	<0.001
Maximal LV wall thickness, mm	22.7 ± 5.4	22.2 ± 5.7	0.61
LAVI ^b	36.9 ± 11.3	41.4 ± 12.5	0.05

On multivariable analysis, the only characteristics associated with LVEF <50% on aficamten were:

- Baseline LVEF ($P=0.044$)
- Permanent atrial fibrillation ($P=0.006$)

* Additional included variables without significant difference: hypertension, diabetes, CAD, beta-blockers, calcium channel blockers, and no background medical therapy.

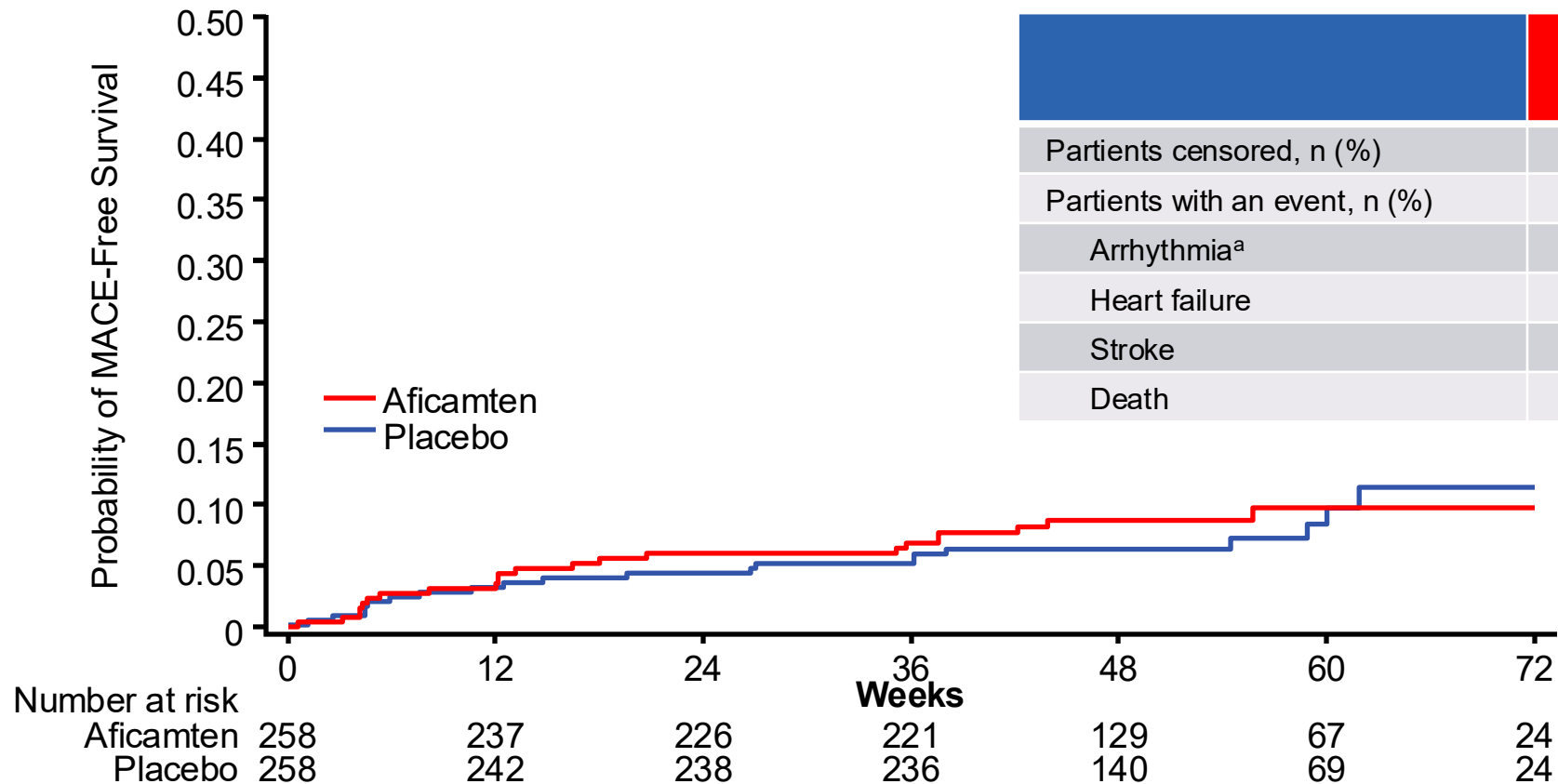
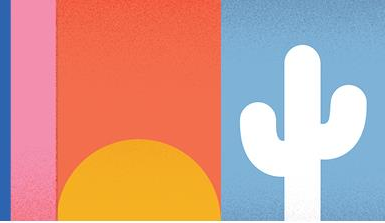


^a 27 patients in aficamten arm and 2 patients in placebo arm.

^b Patients without AF/F at baseline.

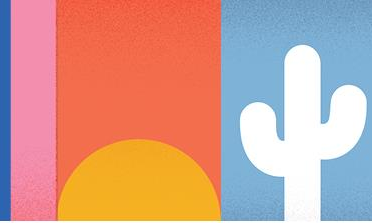
AF/F, atrial fibrillation/flutter; BMI, body mass index; hs, high-sensitivity; CAD, coronary artery disease; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pVO₂, peak oxygen uptake.

Time to First CV Event



	Aficamten n=258	Placebo n=259
Partients censored, n (%)	236 (91.5)	239 (92.3)
Partients with an event, n (%)	22 (8.5)	20 (7.7)
Arrhythmia ^a	17 (6.6)	16 (6.2)
Heart failure	4 (1.6)	1 (0.4)
Stroke	1 (0.4)	2 (0.8)
Death	0	1 (0.4)

Adverse Events

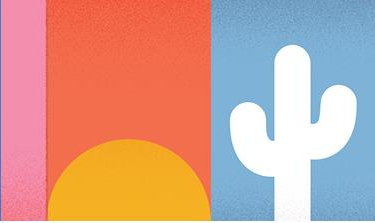


Event, n (%)	Aficamten n=258	Placebo n=259
Any AE	207 (80.2)	217 (84.1)
Any nonfatal AE that led to treatment discontinuation	18 (7.0)	5 (1.9)
Any nonfatal AE that led to early study discontinuation	9 (3.5)	2 (0.8)
Any SAE	52 (20.2)	38 (14.7)
Death	0 (0)	3 (1.2)
Heart Failure	12 (4.7)	3 (1.2)
New AF	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	2 (0.8)	0 (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.

Patients Experiencing HF SAE's Had Comorbidities and Intercurrent Events



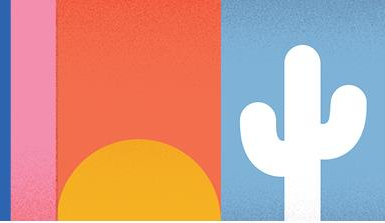
Characteristics and features of SAE's among *aficamten* participants

- Older age (8 out of 12 age ≥ 65)
- Comorbid history of atrial fibrillation in 7 out of 12, and with afib episode preceding HF event in all of these
- Baseline advanced disease or other intercurrent illness (3 out of 12)
- EF < 50% (2 out of 12)

Characteristics and features of SAE's among *placebo* participants

- Comorbid history of atrial fibrillation (2 out of 3)
- Baseline advanced disease or other intercurrent illness (1 out of 3)

ACACIA-HCM: Serious HF Events Occurred During the Automated Titration Phase

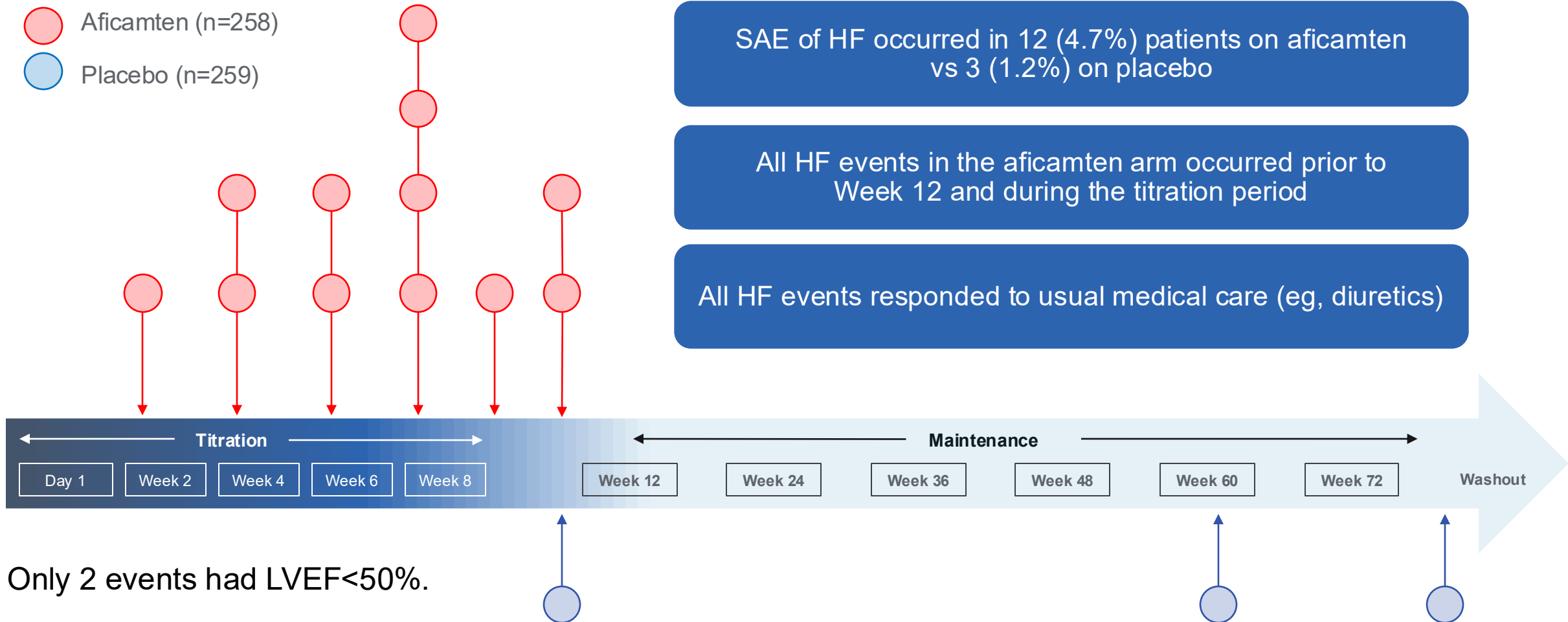


-  Aficamten (n=258)
-  Placebo (n=259)

SAE of HF occurred in 12 (4.7%) patients on aficamten vs 3 (1.2%) on placebo

All HF events in the aficamten arm occurred prior to Week 12 and during the titration period

All HF events responded to usual medical care (eg, diuretics)

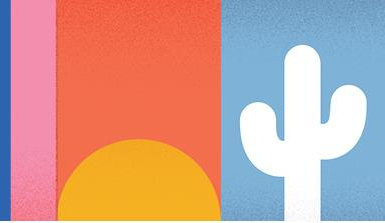


Only 2 events had LVEF<50%.

Conclusions

- Titration of aficamten in patients with nHCM to the maximum tolerated dose based on LVEF alone is generally safe, with reversible serious clinical heart failure due to systolic dysfunction occurring in <1% of patients.
- Dose increments led to predictable changes in plasma aficamten concentration and LVEF, following a similar pharmacokinetic profile seen in oHCM.
- The majority of reduced LVEF events were managed by simple down-titration and patients remained on aficamten.
- Patients with nHCM who present with heart failure symptoms often have an intercurrent illness, events were limited to the titration phase (automated algorithm), and usually have LVEF >50%.
 - 95% of patients on aficamten were titrated without a major issue
- Exploratory analyses of LVEF <50% events suggests some patients (lower baseline LVEF and permanent AF) may be more vulnerable to reduced LVEF with aficamten.

Disclosures & Acknowledgments



- **The ACACIA-HCM trial is funded by Cytokinetics, Incorporated. We thank the following individuals for their contributions to this clinical trial:**
 - Patients and their families.
 - Investigators and study site staff.
 - Data Monitoring Committee members.
 - Steering Committee members: Michael Arad, Roberto Barriaes-Villa, Caroline J. Coats, Edileide de Barros Correia, Juan Pablo Costabel, Perry M. Elliott, Jorge E. Silva Enciso, Carolyn Y. Ho, Gregory D. Lewis, Matthew W. Martinez, Ahmad Masri, Mathew S. Maurer, Michelle Michels, Sumeet S. Mitter, Jesus E. Pino Moreno, Iacopo Olivotto, Anjali T. Owens, Steen H. Poulsen, Florian Rader, Ethan J. Rowin, Junbo Ge, P. Christian Schulze, Mark V. Sherrid, Scott D. Solomon, John A. Spertus, and Charles Teale Sr.
 - Editorial support for the preparation of this presentation was provided by Elyse Smith, PhD, CMPP, on behalf of Envision Medical Communications, and was funded by Cytokinetics, Incorporated.