Safety and Efficacy of Aficamten in Patients with Nonobstructive Hypertrophic Cardiomyopathy: A 96-week Analysis From FOREST-HCM

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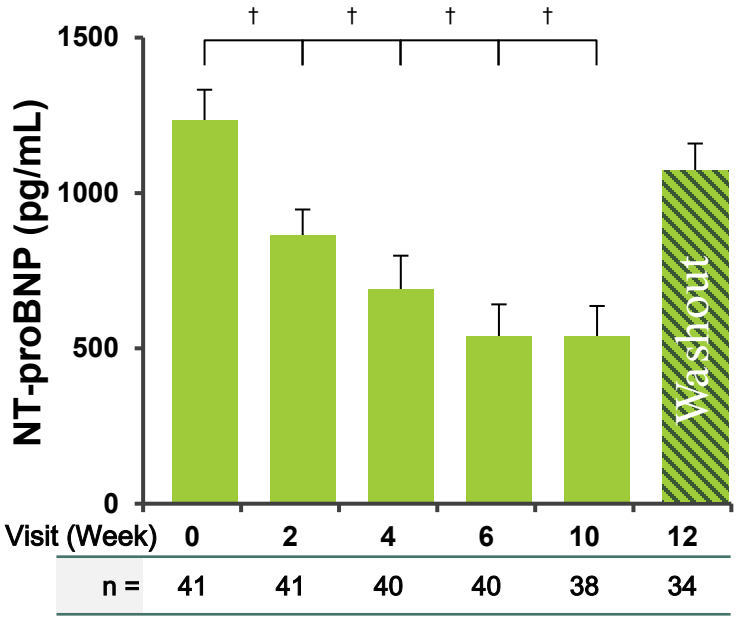
Background and Objective (I)

- Symptomatic nHCM is a common phenotype of HCM, but remains without proven therapies[1,2]
- Aficamten is an oral, investigational, small-molecule selective inhibitor of the cardiac myosin ATPase, reducing contractility by reversibly decreasing excessive myosin-actin cross-bridges
- In REDWOOD-HCM Cohort 4 (NCT04219826) with nHCM patients, aficamten[3]:
  - Was well tolerated over 10 weeks of treatment with infrequent LVEF <50% events
  - Demonstrated improvement in symptoms and biomarkers
- Similar findings were observed over 36 weeks in FOREST-HCM, an open-label extension trial (NCT04848506)[4]

NT-proBNP over 10 Weeks of Aficamten Treatment



Geometric mean NT-proBNP (%CV) decreased at each scheduled visit during treatment, with the proportional change from baseline being highly statistically significant (†*P*<0.0001).

Categorical Changes in KCCQ-CSS at Week 10

56.4% with clinical improvement

- Small (5 to < 10 points)
- Moderate-Large (10 to <20 points)
- Large-very large (≥20 points)
- Worsened (≤ -5 points)
- Unchanged (-5 to < 5 points)

CV, coefficient of variation; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; nHCM, nonobstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

1. Ho CY, et al. *Circulation* 2018;138(14):1387-98. **2.** Butzner M, et al. *Am J Cardiol* 2021;159:107-12. **3.** Masri A, et al. *J Card Fail* 2024;30(11):1439-48. **4.** Masri A, et al. *Eur J Heart Fail* 2024;26(9):1993-8.

Background and Objective (II)

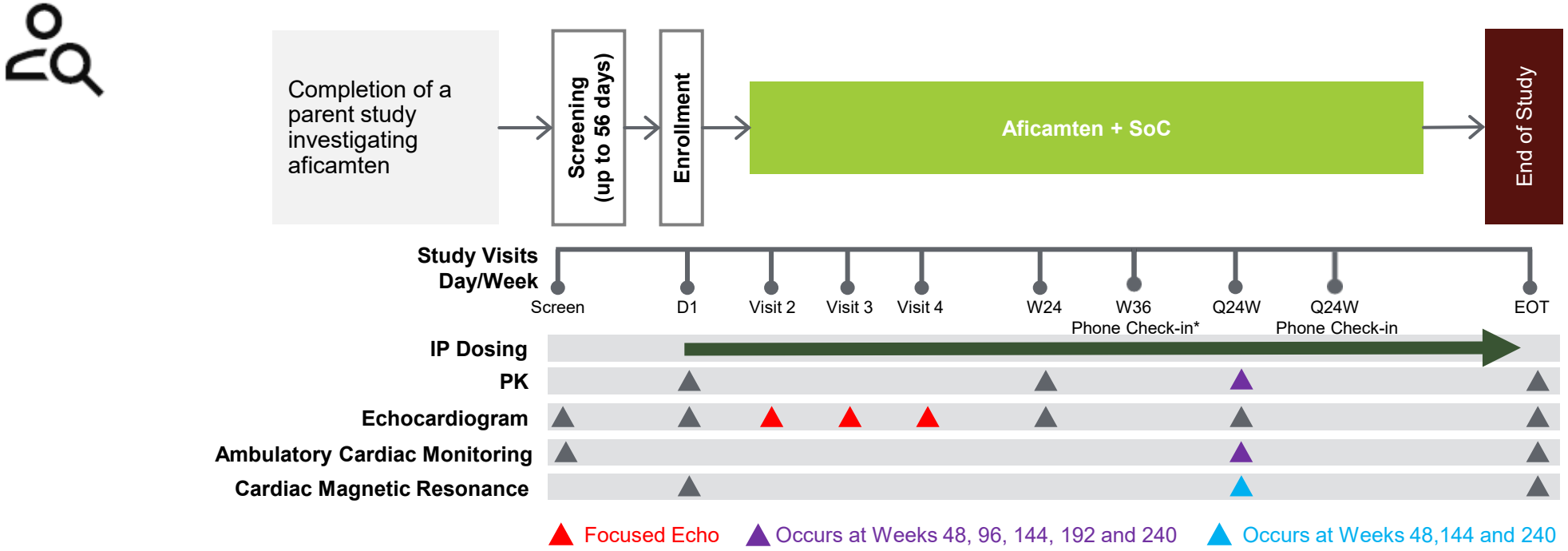
- Recently, ODYSSEY-HCM, a phase 3 trial of mavacamten in patients with symptomatic nHCM, did not meet either of its dual primary endpoints[1] (KCCQ-CSS, Peak VO_2)
- ACACIA-HCM is a phase 3 trial of aficamten in patients with symptomatic nHCM, with results expected in the 1st half of 2026
- Patients from the phase 2 study could enroll in an open-label extension study (FOREST-HCM) and continue to inform on the safety and efficacy of aficamten in nHCM over extended follow-up

OBJECTIVE: **To assess the safety and efficacy of aficamten treatment over 96 weeks in patients with nHCM enrolled in FOREST-HCM**

nHCM, nonobstructive hypertrophic cardiomyopathy.

1. Desai MY, et al. N Engl J Med 2025;393(10):961-972.

Methods



- Patients started on aficamten 5 mg daily; doses were adjusted in 5-mg increments (5–20 mg) at 2-week (±3 day) intervals according to site-read LVEF[a]
  - Increased if LVEF ≥55%; maintained if LVEF 50–54%; decreased by 5 mg if LVEF 40–<50%
- Efficacy and safety were assessed over 96 weeks. Outcome measures included:
  - NYHA class, KCCQ-CSS, LVEF, NT-proBNP, hs-cTnI

[a] Patients enrolled and titrated under Protocol Amendments (PAs) 3 & 4; PA 6 is depicted. *W36 will be a clinic visit for nHCM participants

EOT, end of treatment; hs-cTnI, high-sensitivity cardiac troponin I; IP, investigational product; 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; PK, pharmacokinetics; Q24W, every 24 weeks; SoC, standard of care.

Baseline Characteristics

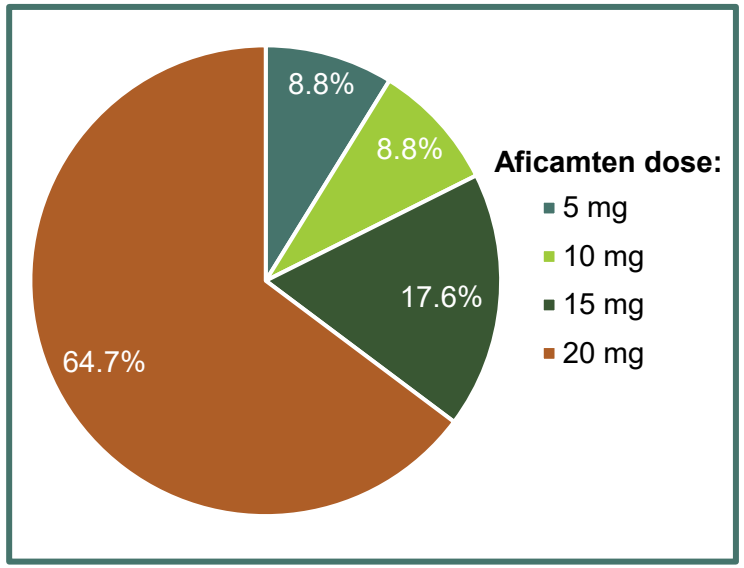
Characteristics	All Patients N=34[a]
Age, mean ± SD, years	57.2 ± 15.3
Female, n (%)	21 (61.8)
White, n (%)	21 (61.8)
Body mass index, mean ± SD, kg/m^2	30.4 ± 7.3
Known history of HCM-causing gene variant or family history of HCM, n (%)	19 (55.9)
Background HCM therapy, n (%)	
Beta-blocker monotherapy	22 (64.7)
Non-dihydropyridine CCB monotherapy	3 (8.8)
No background HCM medications	9 (26.5)

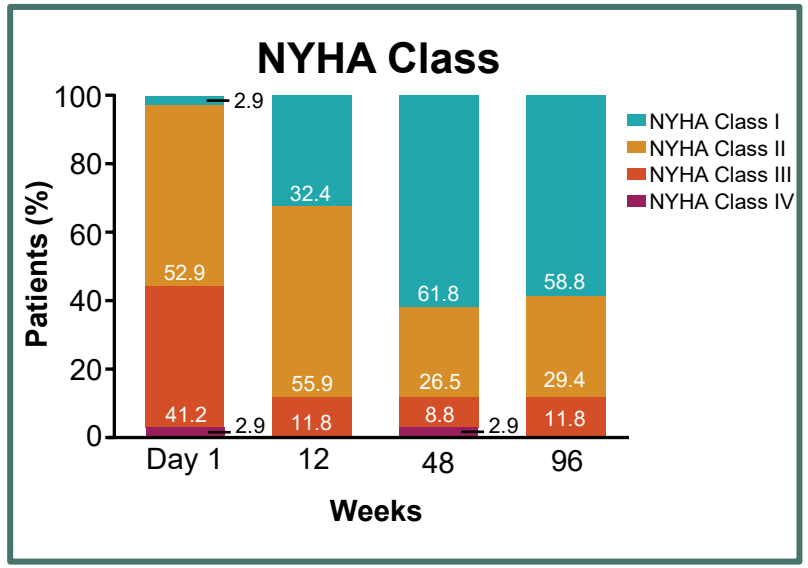
Characteristics	All Patients N=34[a]
Duration of exposure, mean (SD), days	844.3 (72.5)
Total person-years of exposure	78.6
NYHA functional class III–IV, n (%)	15 (44.1)
KCCQ-CSS mean ± SD	67.3 ± 21.8
LVEF (%), mean ± SD	70 (6.1)
Resting LVOT-G, mean ± SD, mmHg	9 (5.4)
Valsalva LVOT-G, mean ± SD, mmHg	11 (8.4)
NT-proBNP, median [QI, Q3], pg/mL	1190 [735, 1735]
hs-cTnI, median [QI, Q3], ng/L	24.9 [9.7, 46.4]

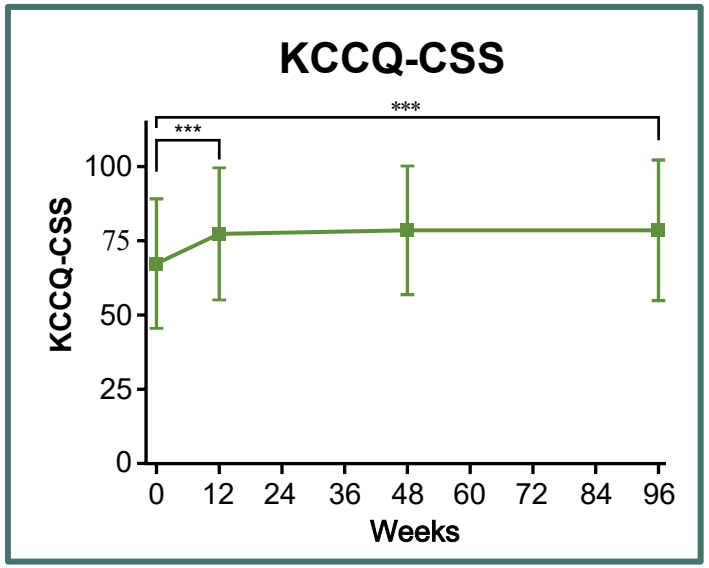
[a] Seven patients were not enrolled from REDWOOD-HCM cohort 4 due to: logistical reasons, non-heart failure-related medical reasons, or death.

CCB, calcium channel blocker; HCM, hypertrophic cardiomyopathy; hs-cTnI, high-sensitivity cardiac troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; Q, quartile.

Results: Aficamten Improved Symptoms and PROs







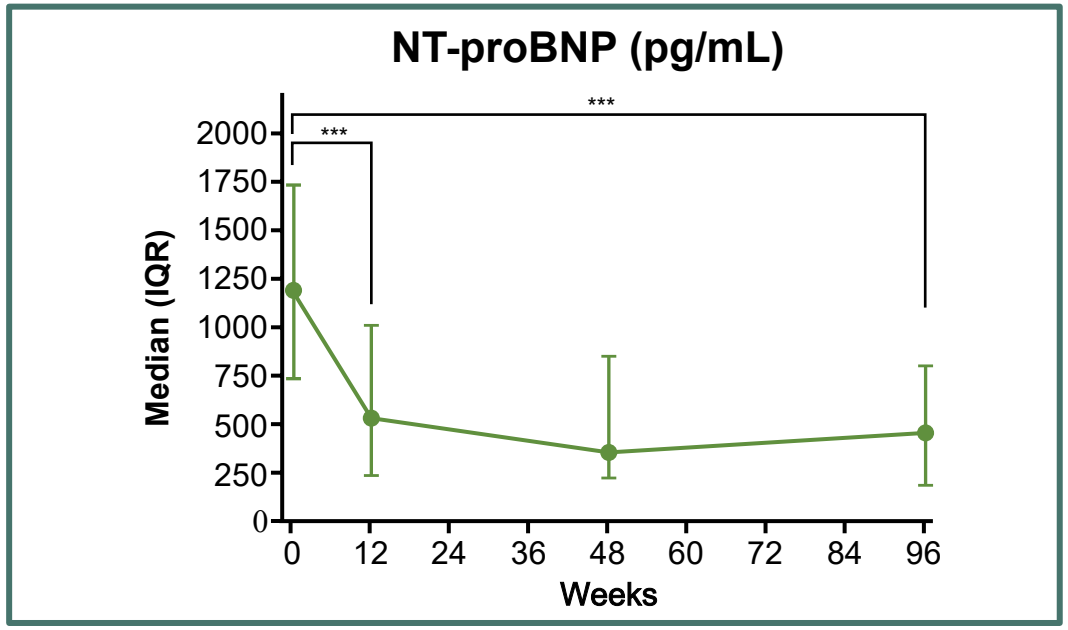
- At the end of titration (Week 6), 82.4% of patients were on the highest available doses (15 or 20 mg), and generally remained on the same dose throughout the maintenance period

- NYHA improved by ≥1 class in 79.4% (27/34) of patients
  - 74.1% (20/27) became asymptomatic
- The proportion of patients with NYHA class III decreased from 41.2% to 11.8% by Week 96

- KCCQ-CSS improved by 11.2 ± 14.3 points from baseline
  - 64.7% (22) of patients reported improvements of ≥5 points by Week 96

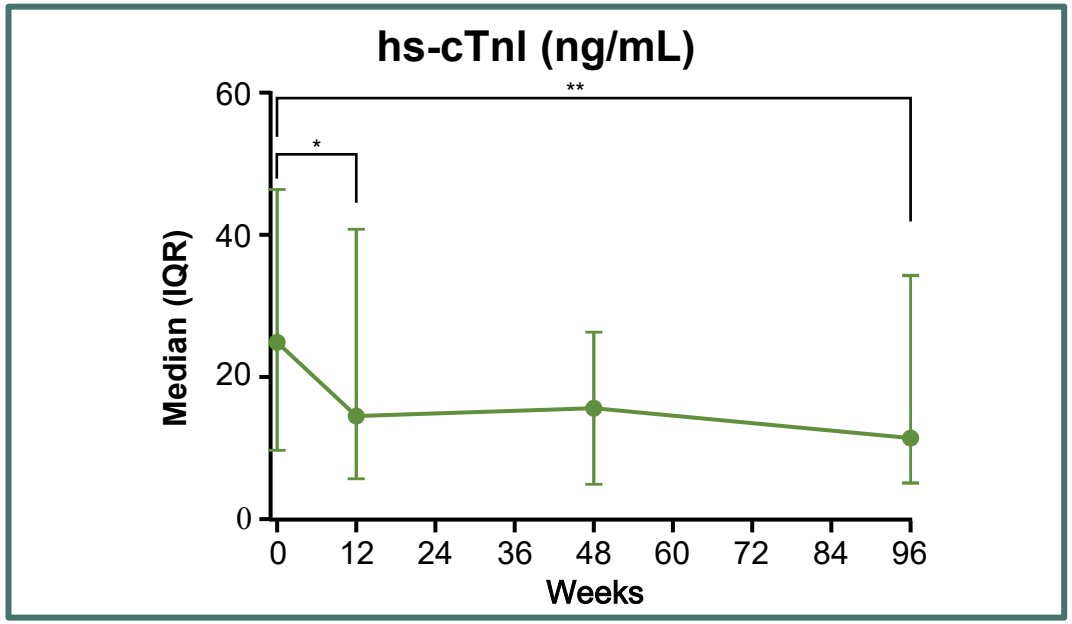
*** *P*<0.0001; Standard Deviation depicted
KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NYHA, New York Heart Association

Results: Aficamten Improved Cardiac Biomarkers



NT-proBNP rapidly declined by Week 12 and remained improved through Week 96:

- Week 12:
  - Δ:−663.0 (−894.8, −431.2) pg/mL
  - Proportional change (95% CI): 0.3 (0.3, 0.4)
- Week 96:
  - Δ: −753.0 (−1034.7, −471.3) pg/mL
  - Proportional change (95% CI): 0.3 (0.2, 0.4)

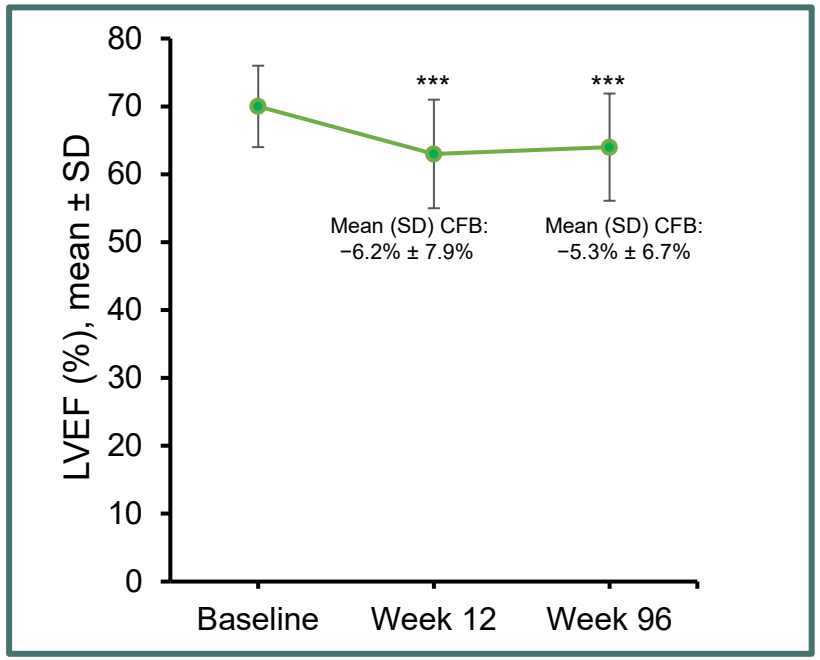


hs-cTnI was reduced by Week 12 and at Week 96:

- Week 12:
  - Δ: −4.3 (−8.2, −0.4) ng/L
  - Proportional change (95% CI): 0.7 (0.6, 0.9)
- Week 96:
  - Δ: −7.3 (−11.7, −2.9) ng/L
  - Proportional change (95% CI): 0.6 (0.5, 0.8)

****P*<0.0001, ***P*<0.01, **P*<0.05
hs-cTnI, high-sensitivity cardiac troponin I; IQR, interquartile range; NT-proBNP, N-terminal pro–B-type natriuretic peptide

Results: Aficamten was Safe and Well Tolerated



- There was a modest reduction in LVEF from baseline hyperdynamic state to within normal range at Week 12
  - This remained stable within normal range up to Week 96

- No patients permanently discontinued treatment
- Over the entire treatment period, 4 patients had LVEF <50% (range: 35%–49%; EAER: 5.4/100 PY)
  - All episodes of LVEF <50% were reversible after down titration or short duration interruption
  - Only 1 patient had LVEF <50% corroborated by the core lab
  - All occurred at the highest doses available (15 or 20 mg)
  - 2 were asymptomatic and managed by down-titration
  - 1 was in the setting of atrial fibrillation
  - 1 was following elective pulmonary vein isolation (with HF symptoms)

*** *P*<0.0001

CFB, change from baseline; EAER, exposure-adjusted event rate; HF, heart failure; LVEF, left ventricular ejection fraction; PY, patient-years

Conclusions

- Aficamten was well tolerated during extended treatment in patients with symptomatic nHCM, with over 80% of patients achieving target doses of 15 or 20 mg
- Extended aficamten treatment led to early and sustained improvements in heart failure symptoms and health status, maintained through 96 weeks
- Cardiac biomarkers indicative of wall stress and myocardial injury showed early reductions that were sustained over the course of treatment
- A low incidence of LVEF <50% and treatment interruptions was observed over 96 weeks of aficamten therapy in patients with nHCM
- These data support the ongoing ACACIA-HCM trial (NCT06081894) evaluating aficamten in nHCM, with results anticipated in the first half of 2026

LVEF, left ventricular ejection fraction; nHCM, nonobstructive hypertrophic cardiomyopathy

Simultaneous publication in *Journal of Cardiac Failure*

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FOREST HCM