Long-Term Efficacy and Safety of *Aficamten* in Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy

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BACKGROUND

- Hypertrophic cardiomyopathy (HCM) is a heterogeneous cardiomyopathy characterized by unexplained left ventricular hypertrophy, hypercontractility, abnormal relaxation and myocardial fibrosis. Two-thirds of patients with HCM have left ventricular outflow tract (LVOT) obstruction.
- First-line therapies for obstructive HCM (oHCM) with beta-blockers, calcium channel blockers, and disopyramide do not address the underlying pathophysiology of the disease.
- *Aficamten* is a next-in-class cardiac myosin inhibitor in development for the treatment of HCM, designed to reduce the hypercontractility that underlies the pathophysiology of HCM.[1]
  - *Aficamten* has been shown to be safe and effective in lowering resting and Valsalva LVOT gradients, improving heart failure symptoms, patient-reported outcomes (Kansas City Cardiomyopathy Questionnaire [KCCQ]), and biomarkers of wall stress and myocardial injury.
- FOREST-HCM (NCT04848506), formerly REDWOOD-HCM OLE, is an ongoing open-label extension study for eligible patients with oHCM or nonobstructive HCM (nHCM) who completed a parent study of *aficamten*.

METHODS

- In FOREST-HCM, patients are required to have **LVEF ≥55%** at screening.
  - Patients with oHCM were initiated on *aficamten* 5 mg and doses adjusted to 5–20 mg by site-read echo-based titration (increased if LVEF ≥55% and Valsalva LVOT peak pressure gradient ≥30 mmHg, decreased if LVEF <50%, and discontinued or interrupted if LVEF <40%).
  - Septal reduction therapy (SRT) eligibility criteria were presence of NYHA class III and peak LVOT gradient ≥50 mmHg.
- Here we report the interim safety and efficacy of *aficamten* in patients with oHCM in FOREST-HCM over 48 weeks.

RESULTS

- From May 2021 to September 2022, 45 patients with oHCM were enrolled.

Baseline Characteristics	Overall (N=45)
Age, mean ± SD (range), y	59.0 ± 12.8 (23–82)
Female, n (%)	26 (58)
Race, n (%)	
White	42 (93.3)
Black	2 (4.4)
Asian	1 (2.2)
BMI, mean ± SD (range), kg/m^2	29.9 ± 6.3 (22–51)
NYHA class, n (%)	
Class II	24 (53.3)
Class III	21 (46.7)

Baseline Characteristics, continued	Overall (N=45)
Positive family history of HCM, n (%)	10 (22.2)
Time since initial HCM diagnosis, mean ± SD (range), y	5.3 ± 5.4 (1–24)
Beta-blocker use, n (%)	35 (78)
Calcium channel blocker use, n (%)	8 (18)
Disopyramide use, n (%)	10 (22)
LVEF[a] at screening, mean ± SD, %	68.9 ± 4.7
LVOT-G[a], rest at screening, mean ± SD, mmHg	47 ± 26
LVOT-G[a], Valsalva at screening, mean ± SD, mmHg	80 ± 30
Eligible for septal reduction therapy, n (%)	19 (42)

[a] Site read of screening echocardiogram

STUDY SCHEMA

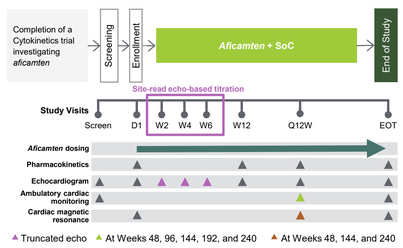
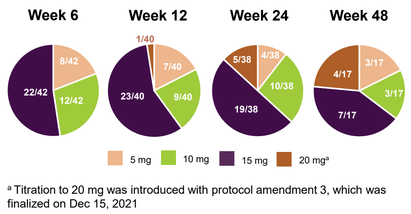


Figure 1: *Aficamten* Dose Achieved



[a] Titration to 20 mg was introduced with protocol amendment 3, which was finalized on Dec 15, 2021

FOREST HCM

FOREST-HCM: Long-Term Efficacy and Safety of *Aficamten* in Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy

In patients with oHCM, *aficamten* was well tolerated and its effects sustained up to 48 weeks

Of 19 patients meeting standard criteria for SRT at baseline, none met those criteria at 48 weeks

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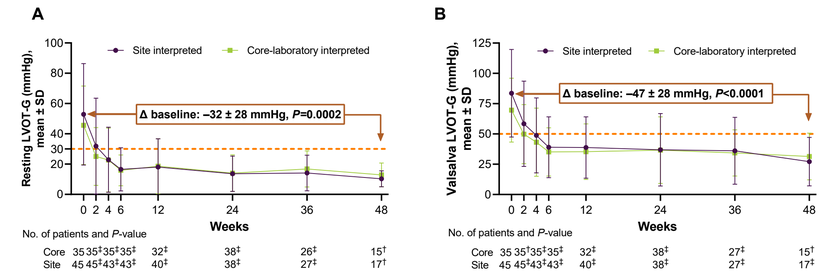
Figure 2: (A) Resting LVOT-G and (B) Valsalva LVOT-G

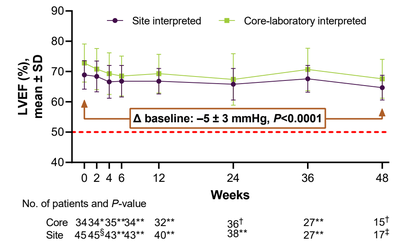
- There was a substantial **reduction in peak resting and Valsalva LVOT-G** from baseline to Week 48 [Δ Resting mean (SD): –32 ± 28 mmHg; Δ Valsalva mean (SD): –47 ± 28 mmHg].



*P<0.05; **P<0.01; †P<0.001; ‡P<0.0001.
Core-laboratory and site-interpreted mean (SD) left ventricular outflow tract (LVOT) gradient (A) at rest and (B) with Valsalva. Boxed brown arrows represent change from baseline in site-read echo values. Orange dashed line represents threshold for designation of severe obstruction.

Figure 3: LVEF

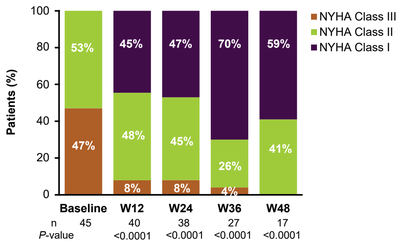
- There was a **modest reduction in LVEF** from baseline to Week 48 (Δ –5 ± 3%) and no patients experienced an *aficamten*-related reduction in LVEF <50%.



§P=0.45; *P<0.05; **P<0.01; †P<0.001; ‡P<0.0001.
Core-laboratory and site-interpreted left ventricular ejection fraction (LVEF). Boxed brown arrows represent change from baseline in site-read echo values. Red dashed line represents low LVEF threshold.

Figure 4: NYHA Class

- There was **substantial improvement** in NYHA class: by Week 48, 88% of patients experienced ≥1 NYHA FC improvement while none had NYHA FC worsening.



Proportion of patients according to NYHA class. *P*-value calculated as ≥1 class improvement vs baseline; using 1-sample test with the null hypothesis that proportion of NYHA improvement is 30%.

SRT Eligibility Criteria

- At baseline, 19 patients (42%) were eligible for SRT per guideline criteria of symptoms and hemodynamics, despite receiving beta-blocker (78%), calcium channel blocker (18%), and disopyramide (22%). At the Week 48 visit, none of these patients met these criteria.

NT-proBNP

- NT-proBNP decreased from baseline to Week 48 (from a geometric mean [CV%] of 651.0 [160.4] to 111.1 [93.4] pg/mL), representing a 70% reduction from baseline (*P*<0.0001).

SAFETY

- *Aficamten* was well tolerated with no treatment-related SAEs reported up to 48 weeks of treatment.
- One patient underwent temporary dose reduction (site error) and another had a temporary dose interruption (recurrent alcohol-induced atrial fibrillation).

CONCLUSIONS

- In this long-term study, treatment with *aficamten* in patients with oHCM was appropriately managed by investigators and was shown to be safe and well tolerated up to 48 weeks.
- Treatment with *aficamten* was associated with rapid and sustained improvements in echocardiographic hemodynamics paralleled by significant improvements in NYHA class.
- *Aficamten* eliminated SRT eligibility in all patients who were guideline-eligible at baseline.
- There were no instances of systolic dysfunction (LVEF <50%) attributed to *aficamten.*
- These data support the continued development of *aficamten*, which is currently being investigated in the Phase III clinical trial SEQUOIA-HCM, and the planned head-to-head comparison of *aficamten* against metoprolol (CY 6032).

Reference: 1. Maron MS, et al. *J Am Coll Cardiol* 2023;81:34-45.

Cytokinetics

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