Efficacy and Safety of *Aficamten* in the First Cohort of Patients With Symptomatic Obstructive Hypertrophic Cardiomyopathy Completing 48-Week Follow-up: Findings From the FOREST-HCM Study

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BACKGROUND

Hypertrophic cardiomyopathy (HCM)
is a characterized by unexplained left ventricular hypertrophy, hypercontractility, abnormal relaxation and myocardial fibrosis. Approximately two-thirds of patients with HCM have left ventricular outflow tract (LVOT) obstruction.

- Standard of care therapy 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]
- Studies of *aficamten* have demonstrated lowering of resting and Valsalva LVOT gradients, improvement of functional class and symptoms, lowering of biomarkers of wall stress and myocardial injury, and being generally well tolerated[1,2]

FOREST-HCM (NCT04848506) is an ongoing open-label extension study for eligible patients with HCM who completed a parent study of *aficamten*

METHODS

- In FOREST-HCM, patients were required to have **LVEF ≥55%** at screening
  - Patients with oHCM were initiated on *aficamten* 5 mg and doses titrated to 5–20 mg by site-read echocardiographic parameters (increased if LVEF ≥55% and Valsalva LVOT peak pressure gradient ≥30 mmHg; decreased if LVEF <50%; and interrupted or discontinued if LVEF <40%)
  - Septal reduction therapy (SRT) eligibility criteria were presence of NYHA class III symptoms and peak LVOT gradient ≥50 mmHg

Here we report the interim safety and efficacy of *aficamten* in 46 patients with oHCM in FOREST-HCM over 48 weeks

RESULTS

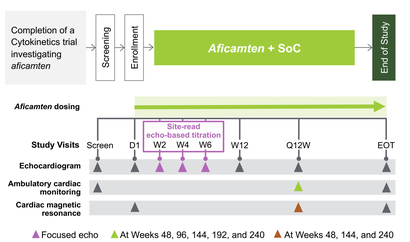
From May 28, 2021 to October 31, 2023, 213 patients with oHCM were enrolled, 46 of whom had completed 48 weeks of follow-up

Baseline Characteristics	Overall (N=46)
Age, mean ± SD (range), y	59.7 ± 12.8 (23–82)
Female, n (%)	26 (56.5)
Race, n (%)	
White	43 (93.5)
Black	2 (4.3)
Asian	1 (2.2)
BMI, mean ± SD (range), kg/m²	29.7 ± 6.1 (22–51)
NYHA class, n (%)	
Class II	24 (52.2)
Class III	22 (47.8)

Baseline Characteristics, continued	Overall (N=46)
Positive family history of HCM, n (%)	8 (17.4)
Years since initial HCM diagnosis, mean ± SD (range)	4.9 ± 5.3 (1–24)
Beta-blocker use, n (%)	36 (78.3)
Calcium channel blocker use, n (%)	8 (17.4)
Disopyramide use, n (%)	9 (19.6)
LVEF[a], mean ± SD, %	69 ± 5
LVOT-G[a], rest at baseline, mean ± SD, mmHg	52 ± 33
LVOT-G[a], Valsalva at baseline, mean ± SD, mmHg	82 ± 35
Eligible for septal reduction therapy, n (%)	19 (41.3)

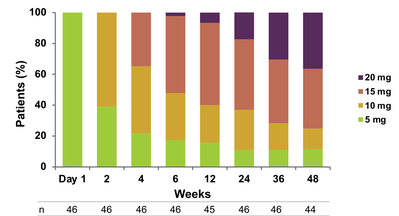
[a]Site read of baseline echocardiogram

STUDY SCHEMA



D, Day; EOT, end of treatment; Q12W, every 12 weeks; SoC, standard of care; W, week

Figure 1: *Aficamten* Dose Achieved



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

Reference: 1. Maron MS, et al. *J Am Coll Cardiol* 2023;81:34-45. **2.** Cytokinetics Incorporated. Cytokinetics announces positive results from SEQUOIA-HCM, the pivotal phase 3 clinical trial of *aficamten* in patients with obstructive hypertrophic cardiomyopathy [media release]; Dec 27, 2023. https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-announces-positive-results-sequoia-hcm-pivotal

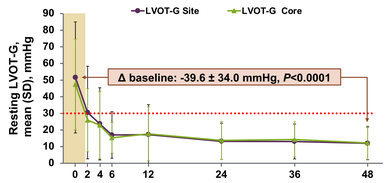
FOREST HCM

Efficacy and Safety of *Aficamten* in the First Cohort of Patients With Symptomatic Obstructive Hypertrophic Cardiomyopathy Completing **48-Week Follow-up**: Findings From FOREST-HCM

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

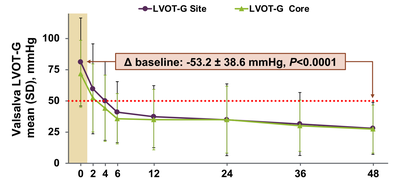
There was a substantial and sustained **reduction in peak resting and Valsalva LVOT-G** from baseline to Week 48 [Δ Resting mean (SD): −39.6 ± 34.0 mmHg; Δ Valsalva mean (SD): −53.2 ± 38.6 mmHg]

Resting LVOT-G



Number of Patients and *P*-value compared with baseline						
Core	45	45[‡]	45[‡]	45[‡]	45[‡]	44[‡]	45[‡]
Site	45	45[‡]	45[‡]	44[‡]	44[‡]	45[‡]	43[‡]	45[‡]

Valsalva LVOT-G



Number of Patients and *P*-value compared with baseline						
Core	45	45[‡]	45[‡]	45[‡]	45[‡]	45[‡]	45[‡]
Site	45	45[‡]	45[‡]	44[‡]	44[‡]	45[‡]	44[‡]	45[‡]

[†]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. Red dashed line represents threshold for definition of obstruction or designation of severe obstruction.

In patients with oHCM, treatment with *aficamten* over 48 weeks appeared safe, improved symptoms and gradients, and reduced the need for SRT

Poster 1075-11; presented at the American College of Cardiology (ACC) 73rd Annual Scientific Sessions Atlanta, GA, USA | April 6–8, 2024

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The FOREST-HCM study was sponsored by Cytokinetics, Incorporated.

Assistance with formatting this poster was provided by SlideSource, Inc. and was funded by Cytokinetics, Incorporated.

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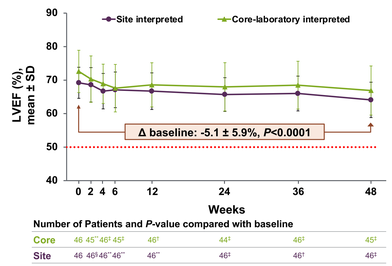
Figure 3: LVEF

There was a **modest reduction in LVEF** from baseline to Week 48 (Δ −5.1 ± 5.9%). Three patients experienced a reduction in LVEF <50% per site-read evaluations (only 1 per core-lab evaluation). None had a concurrent heart failure event.

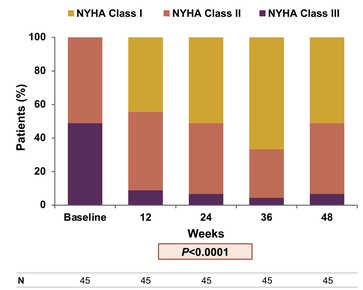


Number of Patients and *P*-value compared with baseline						
Core	46	45[‡]	46[‡]	45[‡]	46[†]	44[‡]	46[‡]	45[‡]
Site	46	46[‡]	46[‡]	46[‡]	46[‡]	44[‡]	46[†]	46[‡]

**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, 82.2% of patients experienced ≥1 NYHA class improvement (*P*<0.0001), whereas none had NYHA class worsening

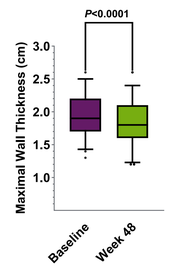


Proportion of patients according to NYHA class. *P*-value calculated as ≥1 class improvement vs baseline; using 1-sample test with empirical placebo response rate of NYHA class that proportion of NYHA improvement is 30%.

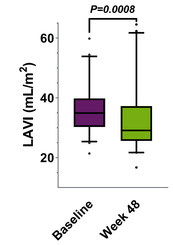
Figure 5: Echocardiographic Structural and Functional Changes

After 48 weeks of treatment, there was a significant improvement [mean (SE) decrease from baseline to Week 48] in maximum wall thickness of −0.12 cm ± 0.02; *P*<0.0001, Left Atrial (LA) Volume Index of −3.5 mL/m² ± 0.98; *P*=0.0008, and Lateral E/e′: of −2.2 ± 0.92; *P*=0.02

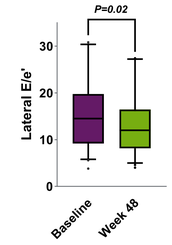
Max Wall Thickness



LA Volume Index



Lateral E/e′



Mean and 95% CI in all figures

SRT Eligibility Criteria

At baseline, 19 (41.3%) patients were eligible for SRT based on symptomatic LVOT obstruction per guidelines, despite receiving beta-blocker (78%), calcium channel blocker (17%), and disopyramide (20%). By 6 months of treatment with *aficamten*, only 1 remained eligible, representing a reduction of SRT-eligibility by 94%.

NT-proBNP

NT-proBNP decreased by 63% from baseline to Week 48 (from a geometric mean [geometric CV%] of 668 [160] to 150 [153] pg/mL; *P*<0.0001)

SAFETY

- *Aficamten* was well tolerated with no treatment-related SAEs reported up to 48 weeks of treatment
- 3 patients underwent dose reduction due to low LVEF (47–49%): 2 were asymptomatic and 1 was in the context of recurrent alcohol-induced atrial fibrillation; this patient also had a temporary dose interruption at time of cardioversion and rhythm control. None had a concurrent heart failure event

CONCLUSIONS

- In this long-term study, treatment with *aficamten* in patients with oHCM was appropriately managed by investigators and appeared to be safe and well tolerated up to 48 weeks
- **Treatment with *aficamten* was associated with rapid, substantial, and sustained improvements in echocardiographic hemodynamics paralleled by improvements in NYHA class and NT-proBNP**
- *Aficamten* eliminated SRT guideline-eligibility in almost all patients who were guideline-eligible at baseline
- There were 3 instances of reversible asymptomatic LVEF <50%, which were manageable by dose down-titration.
- These data support the continued development of *aficamten*, currently investigated in comparison to metoprolol as first-line therapy for oHCM in the Phase III clinical trial MAPLE-HCM (CY 6032)

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Disclosures: SS has received consultant/advisor fees from Bristol Myers Squibb and research grants from Bristol Myers Squibb, Cytokinetics, Novartis, and Actelion Pharmaceuticals. **AM** has received consultant/advisor fees from Tenaya, Attralus, Cytokinetics, Bristol Myers Squibb, Eidos, Pfizer, Alnylam, Haya, Intellia and Ionis, and research grants from Ionis, Akcea, Pfizer, Ultromics, and Wheeler Foundation. **SBH, DJ, SK, FIM, CM, LM, and JW** are employees of Cytokinetics and hold stock in the company,