Efficacy and Safety of *Aficamten* in Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy: Interim Results from the Randomized Evaluation of Dosing with CK-3773274 in Hypertrophic Cardiomyopathy (REDWOOD-HCM) Open-Label Extension Study

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BACKGROUND

- *Aficamten* is a next-in-class cardiac myosin inhibitor that decreases myocardial contractility in patients with obstructive hypertrophic cardiomyopathy (oHCM).
- The Phase 2 trial, REDWOOD-HCM, enrolled 3 cohorts with oHCM:

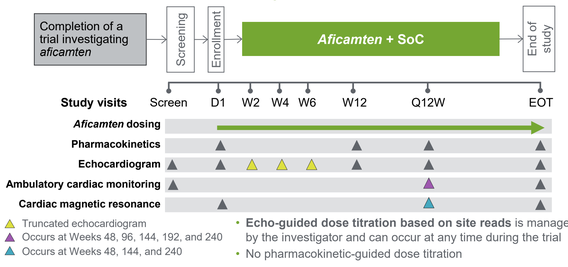
Cohort	N	Population	*Aficamten* doses	Design
1	21	oHCM	5, 10, 15 mg	Placebo-controlled
2	20	oHCM	10, 20, 30 mg	Placebo-controlled
3	13	oHCM on disopyramide	5, 10, 15 mg	Single-arm

- In all 3 cohorts, *aficamten* was well tolerated and treatment was associated with decreases in LVOT gradients (LVOT-G), improvements in NYHA functional class, and reduction in cardiac biomarkers.[1,2]

OBJECTIVES

- The REDWOOD-HCM open-label extension (OLE) is evaluating long-term safety and efficacy of *aficamten* in patients with HCM over 5 years.
- The data cut-off for results presented in this poster was April 18, 2022.

Study schema



△ Truncated echocardiogram
▲ Occurs at Weeks 48, 96, 144, 192, and 240
▲ Occurs at Weeks 48, 144, and 240

- **Echo-guided dose titration based on site reads** is managed by the investigator and can occur at any time during the trial
- No pharmacokinetic-guided dose titration

RESULTS

Figure 1. *Aficamten* dosing over time

Site-read echo-guided dose-titration criteria:
- Up-titration if LVEF ≥50% plus ≥1 of:
  - Resting LVOT-G ≥30 mmHg or
  - Valsalva LVOT-G ≥50 mmHg
- Down-titration if LVEF <50%
- Interruption if LVEF <40%

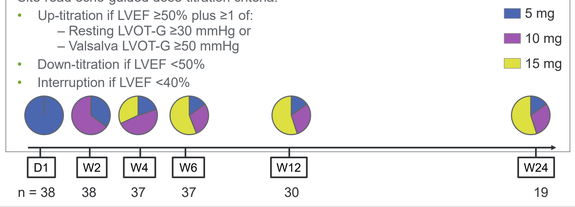
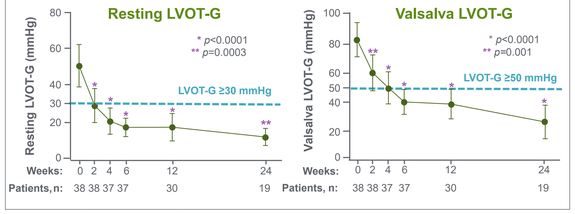


Table 1. Baseline characteristics

Baseline characteristics	N=38
Age, years, mean ± SD [range]	59.9 ± 13.0 [23–82]
Female, n (%)	22 (57.9)
BMI, kg/m^2, mean ± SD [range]	30.1 ± 6.5 [22–51]
NYHA functional class, n (%)	
Class II	18 (47.4)
Class III	**20 (52.6)**
Positive family history of HCM, n (%)	9 (23.7)
Background HCM therapy, n (%)	
Beta blocker	30 (78.9)
Calcium channel blocker	11 (28.9)
Disopyramide	**10 (26.3)**
Echocardiography at screening, mean ± SD [range][a]	
LVEF, %	69.7 ± 4.1 [60–78]
Resting LVOT-G, mmHg	47.0 ± 26.6 [10–95]
Valsalva LVOT-G, mmHg	81.1 ± 29.1 [23–150]
NT-proBNP, pg/mL, geometric mean (%CV) [range]	**628.1** (163.7) [70–8333]
Cardiac troponin I, ng/L, geometric mean (%CV) [range]	**13.8** (287.5) [3.4–2017.1]
Duration on treatment, weeks, mean ± SD [range]	**25.7**±11.7 [5–47]

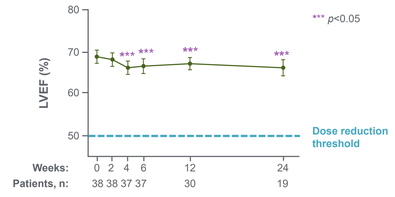
[a] Site read of screening echocardiogram

Figure 2. Rapid and sustained reduction in LVOT-G



Data are mean ± 95% confidence interval (CI). *p*-values based on paired *t*-test comparing baseline and post-baseline values. Echocardiographic data from site reads.

Figure 3. Minimal and stable reduction in LVEF

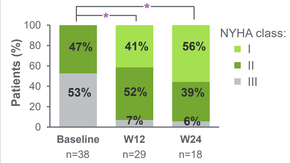


Data are mean ± 95% CI. *p*-values based on paired *t*-test comparing baseline and post-baseline values. Echocardiographic data from site reads.

Figure 4. Improvement in NYHA functional class

Proportion in each class at baseline and Weeks 12 and 24

* *p*<0.0001 for ≥1 NYHA class improvement



Proportion with changes at Weeks 12 and 24

No patient had worsening of NYHA class from baseline

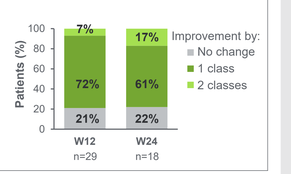
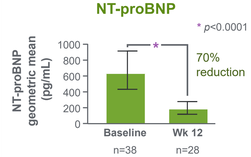
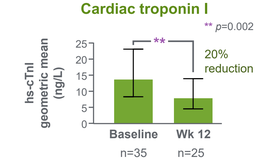


Figure 5. Decrease in cardiac biomarkers

NT-proBNP



Cardiac troponin I



Data are geometric mean ± 95% CI. *p*-values for proportional change from baseline.

Table 2. Safety summary

Patients, n (%)	N=38
≥1 TEAE	28 (74)
≥1 related TEAE	8 (21)
≥1 TESAE	2 (5)
≥1 severe TEAE	1 (3)
TEAE leading to drug interruption	1 (3)
TEAE leading to dose reduction	2 (5)

TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

Table 3. AEs in >1 patient

AE term	n
Headache	4
Dizziness	3
Alopecia	2
Atrial fibrillation	2
Diarrhea	2
Fatigue	2
Parosmia	2
Rash	2
Sinusitis	2

Table 4. Dose interruptions or SAE details

Patient with LVEF <50% and TESAE	History of alcohol-induced atrial fibrillation prior to study with reduced LVEF <50% • On *aficamten* 15 mg, recurrent episode of alcohol-induced atrial fibrillation with similar reduction of LVEF to 47% → ***aficamten* down-titrated** • Subsequently had a failed cardioversion → ***aficamten* interruption** • Patient now back in sinus rhythm on amiodarone, abstinent from alcohol, LVEF 60% with evidence of obstruction and has **re-started *aficamten* at 5 mg**
Patient with temporary down-titration	Investigator was concerned about QTc prolongation in patient with abnormal baseline electrocardiogram →**Temporary *aficamten* down-titration** pending QTc interpretation from the core laboratory • Confirmed that the QTc was normal, and *aficamten* was subsequently increased
Patient with severe TESAE	• Altered mental status prior to planned cardioversion for atrial fibrillation on DOAC, leading to hospitalization → MRI showed presumed embolic stroke • Subsequently diagnosed with congenital cardiac abnormality (secundum atrial septal defect) • No *aficamten* down-titration or interruption

CONCLUSIONS

- In this OLE study of patients with oHCM treated with background medical therapy including disopyramide, *aficamten* was associated with:
  - Significant and sustained reductions in LVOT-G.
  - Substantial improvement in heart failure symptoms (~80% of patients had ≥1 NYHA class improvement).
  - Significant reduction in cardiac biomarkers (NT-proBNP and hs-cTnI).
- *Aficamten* was well tolerated with no events of LVEF <50% attributed to study drug.
  - To date, there has been a single dosing interruption and no permanent discontinuations of *aficamten.*
- The 20-mg dose of *aficamten* is now available for use in the REDWOOD-HCM OLE trial for patients who may not have achieved target gradients on the 15-mg dose.
- These data demonstrate the treatment effect of *aficamten* is durable for up to 6 months.

Future research

- SEQUOIA-HCM (NCT05186818) is an ongoing pivotal Phase 3 trial of *aficamten* in patients with oHCM.

References

1. Maron M, et al. Presented at HFSA; September 10–13, 2021; Denver, CO.
2. Owens AT, et al. *J Am Coll Cardiol* 2022;79:S244.

Acknowledgments

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ABBREVIATIONS: AE, adverse event; BMI, body mass index; CI, confidence interval; D, Day; DOAC, direct oral anticoagulant; EOT, end of treatment; HCM, hypertrophic cardiomyopathy; hs-cTnI, high-sensitivity cardiac troponin I; LV, left ventricular; LVEF, LV ejection fraction; LVOT, LV outflow tract; LVOT-G, LVOT gradient; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive HCM; OLE, open-label extension; Q12W, every 12 weeks; QTc, corrected QT interval; SAE, serious AE; SD, standard deviation; SoC, standard of care; TEAE, treatment-emergent AE; TESAE, treatment-emergent serious adverse event; W, Week.

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