Efficacy and safety of *aficamten* and disopyramide coadministration in obstructive hypertrophic cardiomyopathy: results from REDWOOD-HCM cohort 3

Anjali Tiku Owens,[1] Ahmad Masri, Theodore P. Abraham, Lubna Choudhury, Florian Rader, John D. Symanski, Aslan T. Turer, Timothy C. Wong, Albree Tower-Rader, Caroline Coats, Michael A. Fifer, Iacopo Olivotto, Scott D. Solomon, Hugh Watkins, Laura Robertson, Lisa Meng, Sharon Paige, Amy Wohltman, Stuart Kupfer, Fady I. Malik, Stephen B. Heitner, Martin S. Maron

1. Hospital of the University of Pennsylvania, Philadelphia, PA

BACKGROUND

- HCM is a heterogeneous cardiomyopathy. LVOT obstruction is a strong and independent determinant of progressive HF symptoms.
- Pharmacologic therapy is the first line of treatment for symptomatic oHCM – initially with beta-blockers, then substitution with either verapamil or diltiazem. Disopyramide, a class IA antiarrhythmic drug with strong negative inotropic effects, can lower LVOT-G in patients with oHCM by decreasing LV contractility via altering intracellular calcium dynamics.
- *Aficamten* is an investigational next-generation small molecule allosteric inhibitor of myosin and is designed to reduce the hypercontractility that underlies the pathophysiology of HCM. *Aficamten* has been shown to be safe and effective in lowering LVOT-G in addition to background medical therapy (excluding disopyramide) in REDWOOD-HCM cohorts 1 and 2.
- The safety and efficacy of add-on therapy with *aficamten* in patients with oHCM refractory to all currently available medical therapies, including disopyramide, is unknown.

METHODS

- REDWOOD-HCM cohort 3 included patients with a clinical diagnosis of oHCM (resting LVOT-G ≥50 mmHg or resting LVOT-G ≥30 mmHg and Valsalva LVOT-G ≥50 mmHg) and persistent symptoms despite **background therapy including disopyramide**.
- A **baseline LVEF ≥60%** with stable atrial rhythm for ≥6 months prior to enrollment was required.
- All patients received up to 3 escalating doses of *aficamten* (5, 10, 15 mg once daily), titrated based on echocardiographic guidance at Weeks 2, 4, and 6 (**Study Schema**).
- Overall, the treatment duration was 10 weeks with a 4-week follow-up period after the last dose.

RESULTS

Baseline Characteristics

- **13 patients** were enrolled (59±14 years of age; 54% female) with NYHA class II (n=5) and III (n=8). Patients had evidence of LV hypercontractility (LVEF 70±7%), severe LVOT obstruction (resting: 52±22 mmHg; Valsalva: 97±36 mmHg) and elevated NT-proBNP (GeoMean 1051 [%CV 147 pg/mL]) (**Table 1**).

Change in LVOT-G and NT-proBNP

- There was a **substantial reduction in peak resting and Valsalva LVOT-G** from baseline to the end of the 10-week treatment period; mean values at Week 10 were: resting 23.6±17.0 mmHg, Valsalva 50.1±24.7 mmHg (**Fig 1**). There was a **modest reduction in LVEF** from baseline (74±8%) to Week 10 (69±7%) (**Fig 2**).
- **6 of 13 (46%) patients experienced a complete hemodynamic** response to *aficamten* by Week 10. The remaining 7 (54%) would be eligible for higher doses of *aficamten* (LVEF >50% and persistent LVOT obstruction) (**Fig 3**).
- Patients experienced a **substantial reduction in NT-proBNP** (GeoMean of proportional change from baseline to Week 10 = 0.48 [%CV 78.24]) and apparent **reductions in hs-troponin I** by Week 10 (**Figs 5 & 6**).

Improvement in HF Symptoms

- **11 of the 13 (85%) patients experienced ≥1 improvement in NYHA class** (**Fig 4**).
- The 2 patients without an improvement in NYHA showed resolution of resting LVOT-G, but persistent Valsalva LVOT-G >50 mmHg at Week 10. Both patients would be eligible for titration to a higher dose at Week 10.

Safety

- There were no dose interruptions or treatment discontinuations, and no serious adverse events. Coadministration of *aficamten* along with disopyramide and an AV nodal blocker did not result in any significant changes in QT interval, blood pressure, or heart rate.

CONCLUSIONS

- In this open-label cohort in oHCM patients with continued HF symptoms and persistent LVOT obstruction despite AV nodal blocking agents and disopyramide, **the addition of the next-generation myosin inhibitor *aficamten* at 5, 10, and 15 mg was well tolerated and provided substantial decrease in resting and provocable LVOT gradients.**
- The beneficial hemodynamic effect of *aficamten* **was mirrored by a substantial improvement in HF symptoms in the majority of patients and decreased levels of NT-proBNP.**

REDWOOD HCM

REDWOOD-HCM cohort 3: evidence for clinical efficacy of *aficamten* in patients with obstructive HCM and HF symptoms refractory to maximal medical therapy, including disopyramide

In oHCM patients refractory to optimal medical therapy, the addition of ***aficamten*** **substantially reduced LVOT gradient and improved HF symptoms**

For more information, email anjali.owens@pennmedicine.upenn.edu

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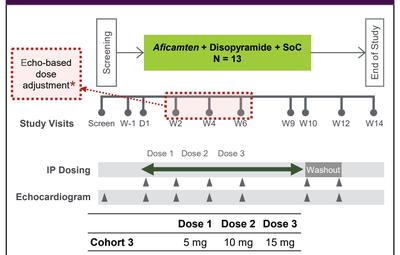
DISCUSSION

- *Aficamten* appears to be safe and exert a pharmacodynamic effect even in patients with the most recalcitrant oHCM.
- Higher doses than those studied in this cohort are likely to produce a greater hemodynamic response than seen in this study. These higher doses are being tested in SEQUOIA-HCM, the pivotal Phase 3 study of *aficamten* in oHCM.
- These data support further longitudinal investigations to determine if *aficamten* may provide additional clinical benefit for this subgroup of patients with HCM who are otherwise refractory to all currently available medical therapies.
- Patients are eligible for participation in the 5-year long-term extension study (REDWOOD-HCM OLE) and the associated cardiac MRI sub-study.

Study Schema: REDWOOD-HCM Cohort 3



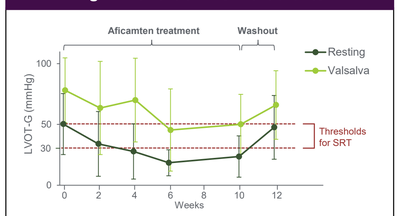
* Dose increase if LVEF ≥50% and resting LVOT-G ≥30 mmHg and/or Valsalva LVOT-G ≥50 mmHg; dose maintained if LVEF ≥50% and resting LVOT-G <30 mmHg; dose decrease if LVEF <50%, and drug discontinuation if LVEF <40%.
IP, investigational product

TABLE 1: Patient Characteristics

Characteristic	Cohort 3 (N = 13)	Cohort 1 (N = 21)	Cohort 2 (N = 20)
Age (years), Mean (SD) [Range]	**59 (14) [23, 82]**	57 (12) [33, 69]	57 (13) [35, 78]
Female, n (%)	**7 (54)**	10 (48)	13 (65)
BMI (kg/m²), Mean (SD)	**30 (6)**	29 (5)	30 (7)
NYHA Class, n (%)			
Class II	**5 (38.5)**	16 (76.2)	12 (60.0)
Class III	**8 (61.5)**	5 (23.8)	8 (40.0)
Beta-Blocker Use, n (%)	**11 (84.5)**	16 (76.2)	16 (80.0)
LVEF* at Screening (%), Mean (SD)	**70 (7)**	73 (8)	72 (7)
LVOT-G*, Rest at Screening (mmHg), Mean (SD)	**52 (22)**	61 (28)	67 (30)
LVOT-G*, Valsalva at Screening (mmHg), Mean (SD)	**97 (36)**	88 (25)	93 (35)
NT-proBNP (pg/mL), GeoMean (%CV)	**1050.6 (147.3)**	368.5 (255.0)	573.8 (145.5)

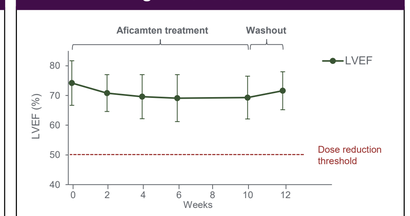
* Site read of screening echocardiogram

Fig 1: Cohort 3 LVOT Gradients



Values are mean ± SD. Core-lab read echocardiograms. SRT, septal reduction therapy

Fig 2: Cohort 3 LVEF



Values are mean ± SD. Core-lab read echocardiograms.

Fig 3: Hemodynamic Response

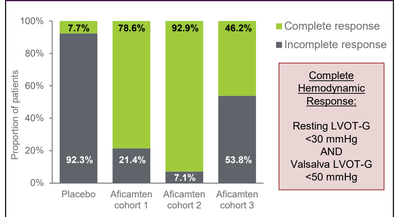
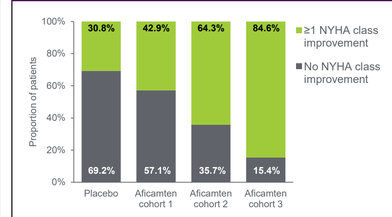
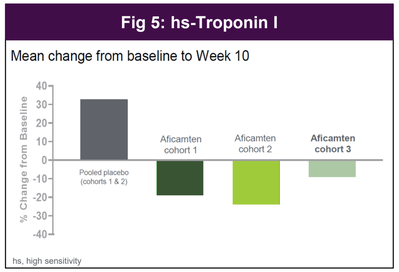


Fig 4: NYHA Response



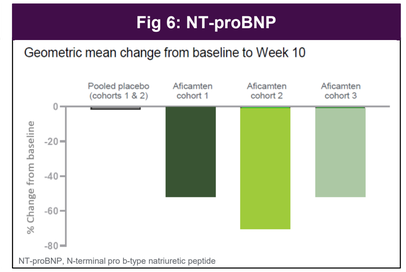
NYHA, New York Heart Association

Fig 5: hs-Troponin I



hs, high sensitivity

Fig 6: NT-proBNP



NT-proBNP, N-terminal pro b-type natriuretic peptide

ABBREVIATIONS: GeoMean, geometric mean; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricular; LVEF, LV ejection fraction; LVOT, LV outflow tract; LVOT-G, LVOT gradients; oHCM, obstructive HCM.