Aficamten in Patients with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (REDWOOD-HCM Cohort 4)

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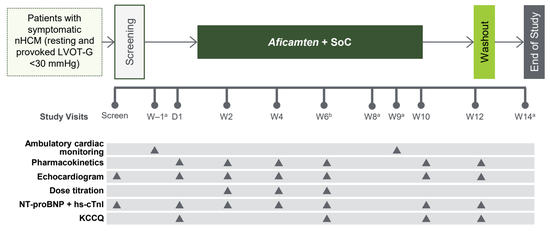
BACKGROUND

- Patients with non-obstructive hypertrophic cardiomyopathy (nHCM) represent a significant subset of HCM patients (~30%), and when symptomatic, have few therapeutic options.
- Other than cardiac transplantation, there are no proven medical therapies that improve functional capacity, symptoms, or outcomes.
- *Aficamten* is a small molecule, allosteric inhibitor of cardiac myosin designed to reduce the hypercontractility that underlies the pathophysiology of HCM.
- REDWOOD-HCM is a phase 2 dose-finding study, and Cohort 4 is designed to evaluate the safety of *aficamten* in patients with symptomatic nHCM.

METHODS

- Eligible participants with nHCM were enrolled in an open-label fashion according to these key eligibility criteria: NYHA II/III with LVEF ≥60%; absence of rest or provoked LVOT gradient (<30 mmHg); NT-proBNP ≥300 pg/mL; and no history of LVEF <45%.
- Treatment duration was 10 weeks with a 2-week washout period (**Figure 1**).
- *Aficamten* doses (5, 10, or 15 mg daily), starting with an initial dose of 5 mg, were adjusted according to LVEF on site-read echocardiographic guidance at Weeks 2 and 4 (**Figure 2**).
- NYHA class, LVEF, cardiac biomarkers (NT-proBNP and hs-cTnI), and safety were assessed.
  - Data are presented for 40 patients up to Week 10 and 35 patients at Week 12 (at data cutoff 5 patients had completed treatment and 1 died).

FIGURE 1 – Study Schema



[a] Telephone visit [b] At Week 6, patients can only be down-titrated.

FIGURE 2 – Titration Algorithm

Up-Titration if:
LVEF ≥55%

Maintain if:
LVEF 50–54%

Down-Titration if:
LVEF <50%

Discontinue if:
LVEF <40%

TABLE 1 – Baseline Characteristics

41 patients were enrolled between March and November 2022

Baseline characteristic	N=41
Age, mean ± SD, y	55.9 ± 15.8
Sex, female, n (%)	24 (58.5)
Race, n (%)	
White	28 (68.3)
Black or African American	8 (19.5)
Asian	2 (4.9)
Other	3 (7.3)
BMI, mean ± SD, kg/m^2	30.0 ± 7.1
NYHA class, n (%)	
Class II	21 (51.2)
Class III	20 (48.8)
LVEF, mean ± SD, % Site-read	68.1 ± 5.5
NT-proBNP, GeoMean (%CV), pg/mL	1254 (80.1)
hs-cTroponin I, GeoMean (%CV), ng/L	28.7 (317.6)

REDWOOD-HCM Cohort 4 is the first study evaluating dosing, safety, and efficacy of *aficamten* in patients with symptomatic non-obstructive hypertrophic cardiomyopathy (nHCM)

Aficamten was well-tolerated and resulted in significant improvements in heart failure symptoms and biomarkers in nHCM patients

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TABLE 2 – Summary of Treatment-Emergent Adverse Events

n (%)	All patients (N=41)
Patients reporting ≥1 TEAE	27 (66)
Patients with treatment-emergent SAEs	3 (7.3)
Patients with fatal TEAEs	1 (2.4)[a]
Patients with TEAEs leading to drug interruption/drug discontinuation	1 interruption[b]
Patients with severe TEAEs	3 (7.3)
Patients with moderate TEAEs	15 (37)
Patients with AEs related to study drug (per Investigator)	4 (9.8)

[a] Fatal TEAE was not related to study drug.
[b] Patient self-interrupted study drug for 2 days because of palpitations (AE) in setting of upper respiratory infection (AE). Patient restarted study drug upon instruction from site. Palpitations resolved.

FIGURE 3

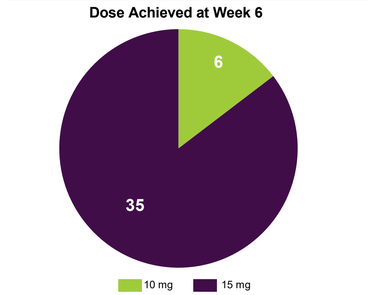

Figure 3: 35 patients (85%) achieved daily *aficamten* dose of 15 mg; 6 patients (15%) achieved 10 mg; 1 patient on 10 mg did not complete the titration period because *aficamten* was discontinued due to personal reasons.

FIGURE 4

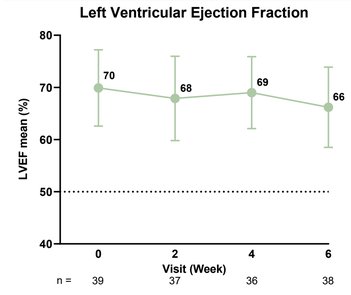

Figure 4: LVEF mean (SD) core lab assessments during titration period. Although LVEF decreased modestly, no LVEF was <50% during this period.

FIGURE 5

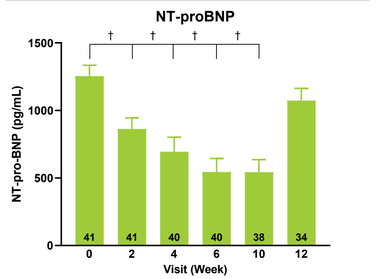

Figure 5: Geometric mean NT-proBNP (%CV) decreased at each scheduled visit with the proportional change from baseline being highly statistically significant († *P*<0.0001).

FIGURE 6

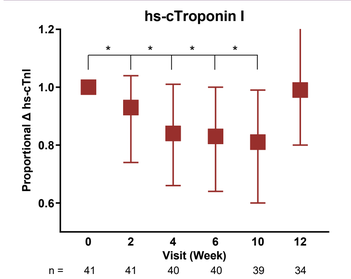

Figure 6: hs-cTnI decreased significantly at each study visit compared to baseline (* *P*<0.05). After the 2-week washout, cardiac biomarkers returned to baseline.

FIGURE 7

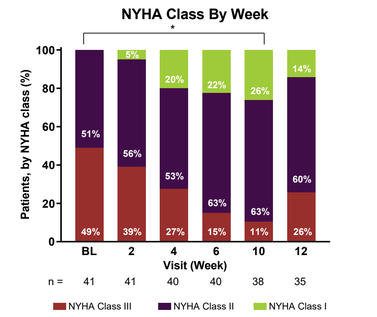

Figure 7: NYHA class improved during treatment (* *P*<0.05): 22 of 41 (54%) patients experienced a change of ≥1 NYHA class, including 12 patients who improved from class III to II; 2 patients improved from class III to I; and 8 from class II to I.

SAFETY

- *Aficamten* was well-tolerated overall (**Table 2**):
  - 85% of the cohort achieved a 15 mg dose.
  - 66% had ≥1 TEAE.
  - There were no drug discontinuations due to AEs: 1 patient had a dose reduction to 10 mg for AE of fatigue at Week 9; 1 had a dose interruption for 2 days due to AE of palpitation.
  - 3 patients had SAEs: bronchitis, new onset atrial fibrillation, cardiac arrest. None were deemed related to *aficamten* by the Investigator.
- 3 patients (7.3%) had LVEF <50% at Week 10 (EOT): 2 in patients with permanent atrial fibrillation, 1 of whom reported palpitations that required adjustment of rate-control medications. No AEs of heart failure were reported. All 3 patients returned to baseline LVEF by Week 12.

CONCLUSION

- REDWOOD-HCM Cohort 4 is the first study exploring dosing and tolerability of *aficamten* in patients with non-obstructive HCM.
- *Aficamten* was well tolerated overall, with modest on-target reductions in LVEF in response to *aficamten* over 10 weeks.
- There was significant improvement in heart failure burden in most patients with nHCM accompanied by improvement in cardiac biomarkers during open-label therapy.
- These results support further study of *aficamten* in a larger, longer-term trial of patients with symptomatic nHCM.

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