

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

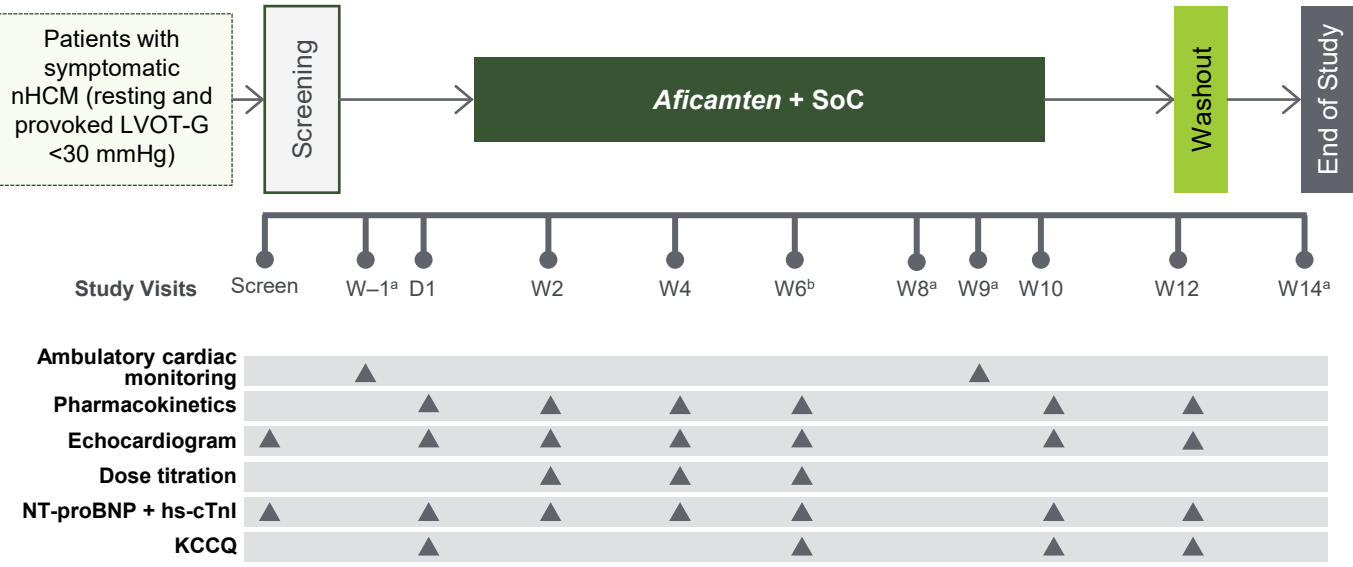


FIGURE 2 – Titration Algorithm

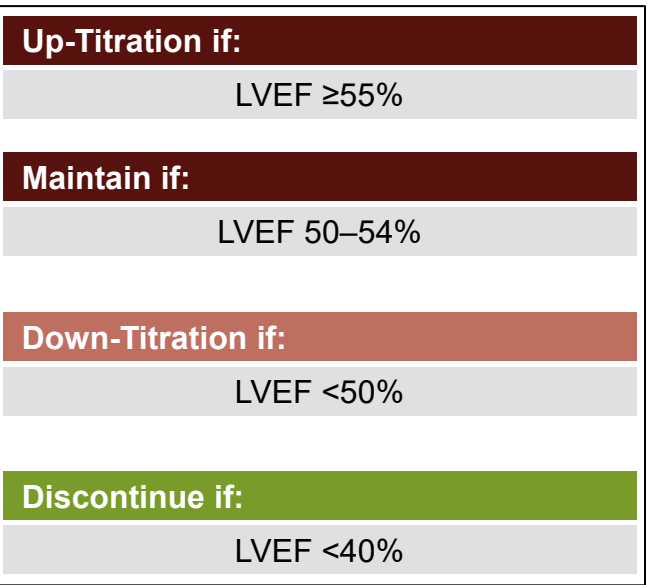


TABLE 1 – Baseline Characteristics

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/mL	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

Dose Achieved at Week 6

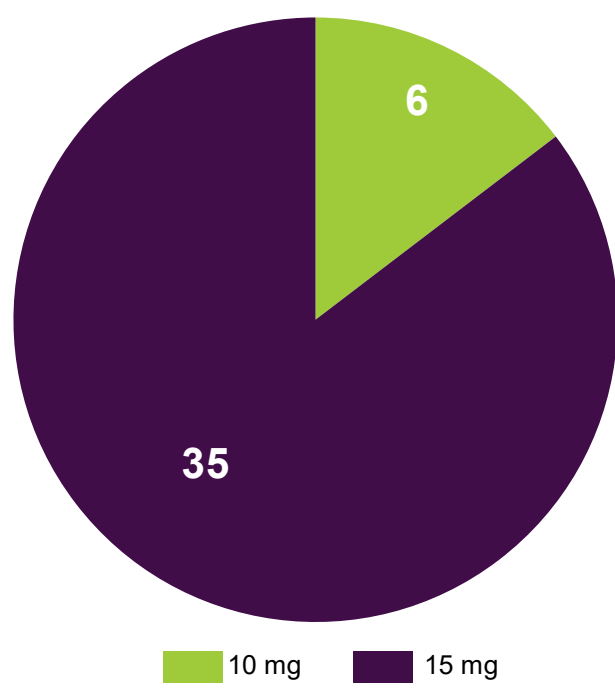


Figure 3: 35 patients (85%) achieved daily *aficamten* dose of 15 mg; 6 patients (15%) achieved 10 mg; 1 patient on 10 mg did not complete the titration period because *aficamten* was discontinued due to personal reasons.

FIGURE 5

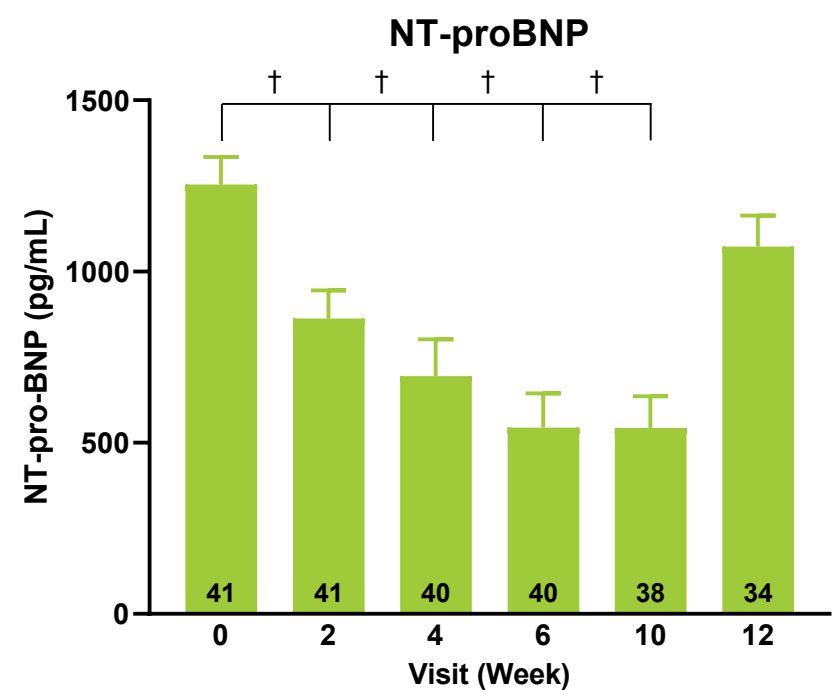


Figure 5: Geometric mean NT-proBNP (%CV) decreased at each scheduled visit with the proportional change from baseline being highly statistically significant († *P*<0.0001).

FIGURE 7

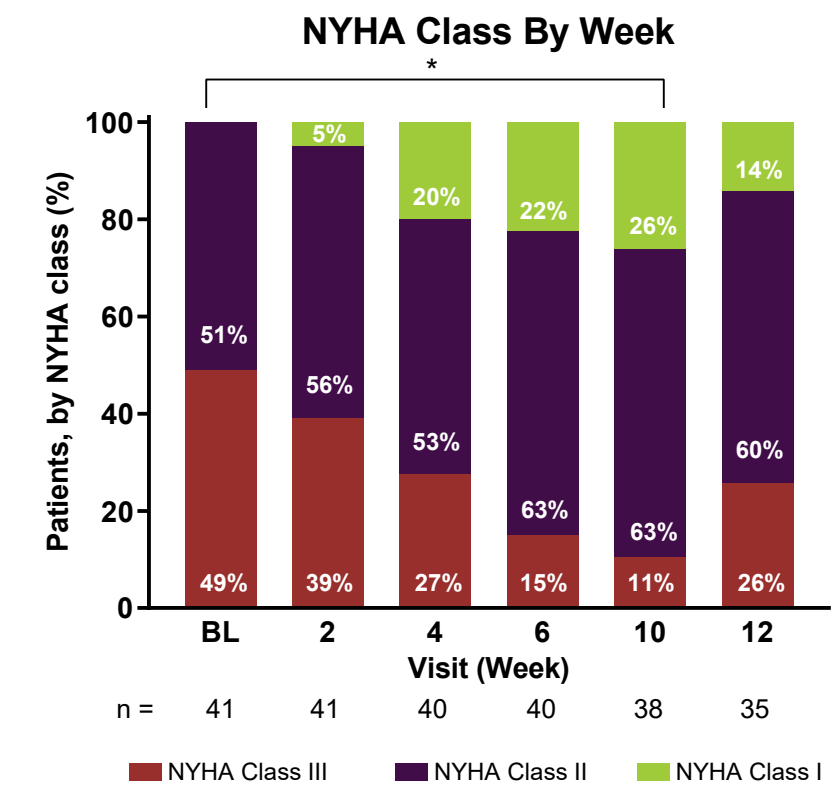


Figure 7: NYHA class improved during treatment (* *P*<0.05): 22 of 41 (54%) patients experienced a change of ≥1 NYHA class, including 12 patients who improved from class III to II; 2 patients improved from class III to I; and 8 from class II to I.

FIGURE 4

Left Ventricular Ejection Fraction

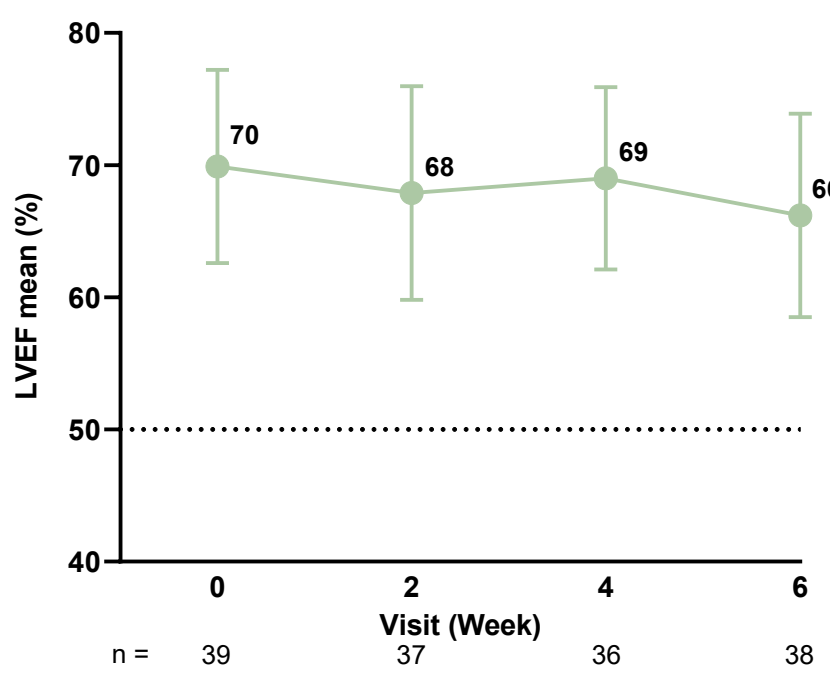


Figure 4: LVEF mean (SD) core lab assessments during titration period. Although LVEF decreased modestly, no LVEF was <50% during this period.

FIGURE 6

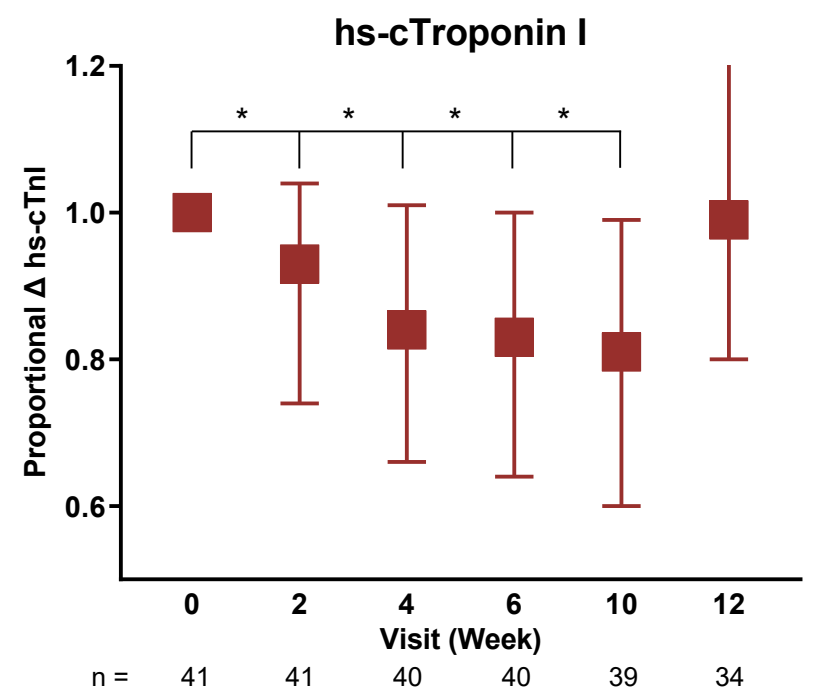


Figure 6: hs-cTnI decreased significantly at each study visit compared to baseline (* *P*<0.05). After the 2-week washout, cardiac biomarkers returned to baseline.

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.

Disclosures: Dr Masri 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. Dr Maron has received consultant/advisor fees from Imbria and Takeda, and steering committee fees for REDWOOD-HCM from Cytokinetics.



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