Evaluation of *Aficamten* in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy: REDWOOD-HCM Cohort 4

An open label, dose finding study evaluating the safety and efficacy of *aficamten*, the next-in-class cardiac myosin inhibitor, in patients with non-obstructive HCM

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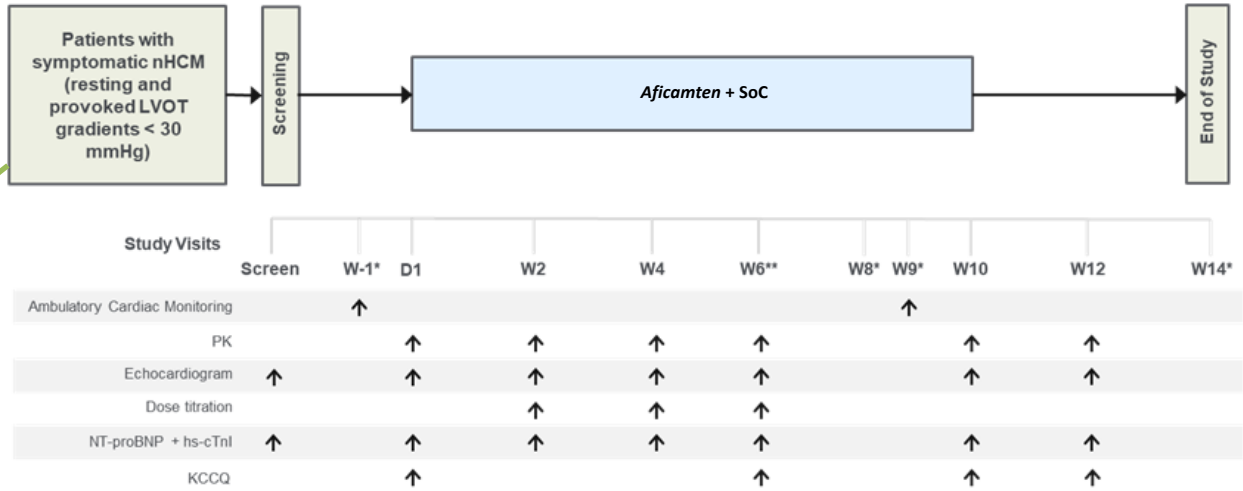
Background

- Patients with non-obstructive hypertrophic cardiomyopathy (nHCM) represent a sizeable subset of HCM patients (~30%), for whom there are no specific medical therapies.

- *Aficamten* is a next-in-class cardiac myosin inhibitor designed to target the myocardial hypercontractility and impaired relaxation that is responsible for the pathophysiology resulting in generation of symptoms and functional impairment and is being explored in this study as a potential novel therapy for nHCM.

REDWOOD-HCM: Non-obstructive HCM Cohort 4



Available Doses: 5, 10, 15 mg

Up-Titration if:
LVEF ≥ 55%

Maintain if:
LVEF 50-54%

Down-Titration if:
LVEF < 50%

Discontinue if:
LVEF < 40%

- New York Heart Association (NYHA) class II/III
- Left ventricular ejection fraction (LVEF) ≥60%
- N-terminal pro–B-type natriuretic peptide (NT-proBNP) >300 pg/mL

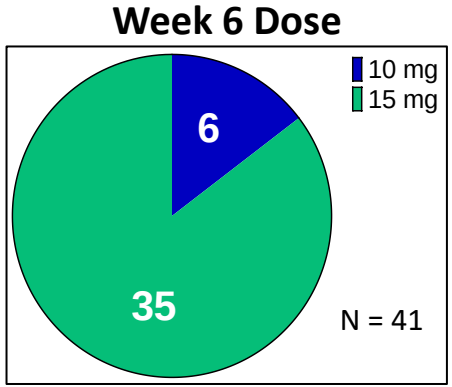
Baseline Characteristics

	N=41
Age, mean (SD; Range), y	55.9 (15.8; 22-82)
Sex, female, n (%)	24 (58.5)
Race, n (%)	
White	27 (65.9)
Black or African American	8 (19.5)
Asian	2 (4.9)
Other/unknown	4 (9.8)
BMI, mean (SD), kg/m^2	30.0 ± 7.1
NYHA class, n (%)	
Class II	21 (51.2)
Class III	20 (48.8)
KCCQ-CSS	67.6 (20.4)
SAQ-AF *	63.6 (10.8)
Atrial fibrillation/flutter, n (%)	4 (9.8)

	N=41
Background HCM Therapy	
Beta-blocker, n (%)	30 (73.2)
Calcium channel blocker, n (%)	4 (9.8)
NT-proBNP, Median (IQR), pg/mL	1103 (755 - 2037)
hs-cTroponin I, Median (IQR), ng/L	21.6 (9.5 - 67.7)
Echocardiography	
LVEF (%, SD)	69.8 (7.2)
Lateral e', mean (SD), cm/s	7.3 (2.9)
E/e', mean (SD)	11.6 (5.0)
Left atrial volume index, mean (SD), ml/m2	34.0 (11.3)

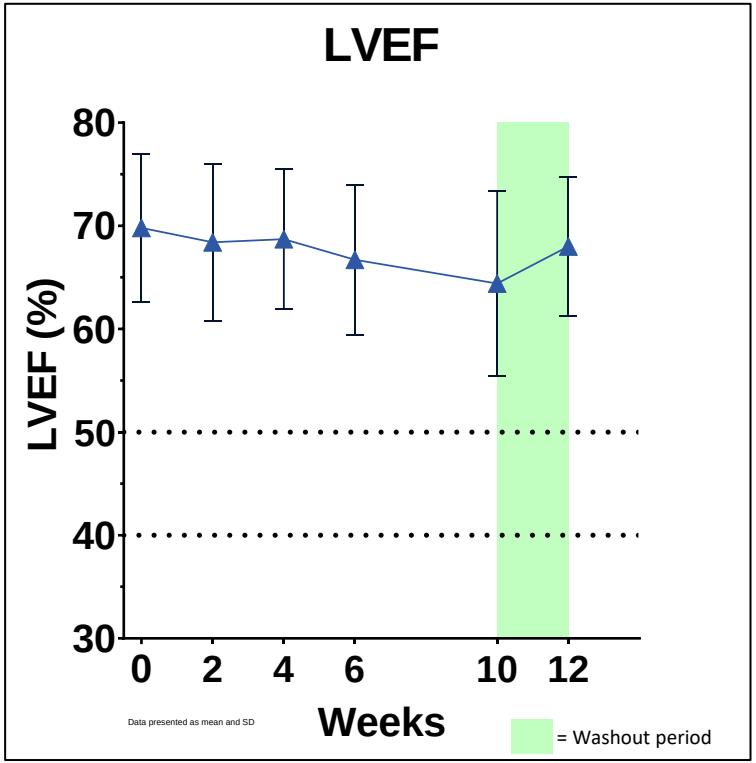
* N = 14 patients with baseline angina (SAQ AF ≤ 80)

Dose Titration and Left Ventricular Ejection Fraction

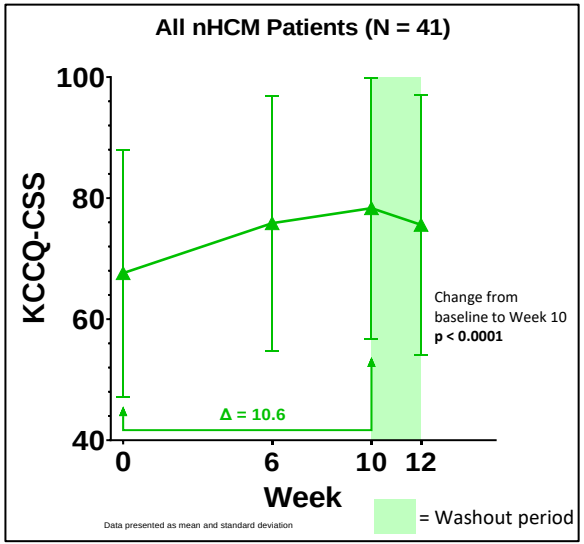


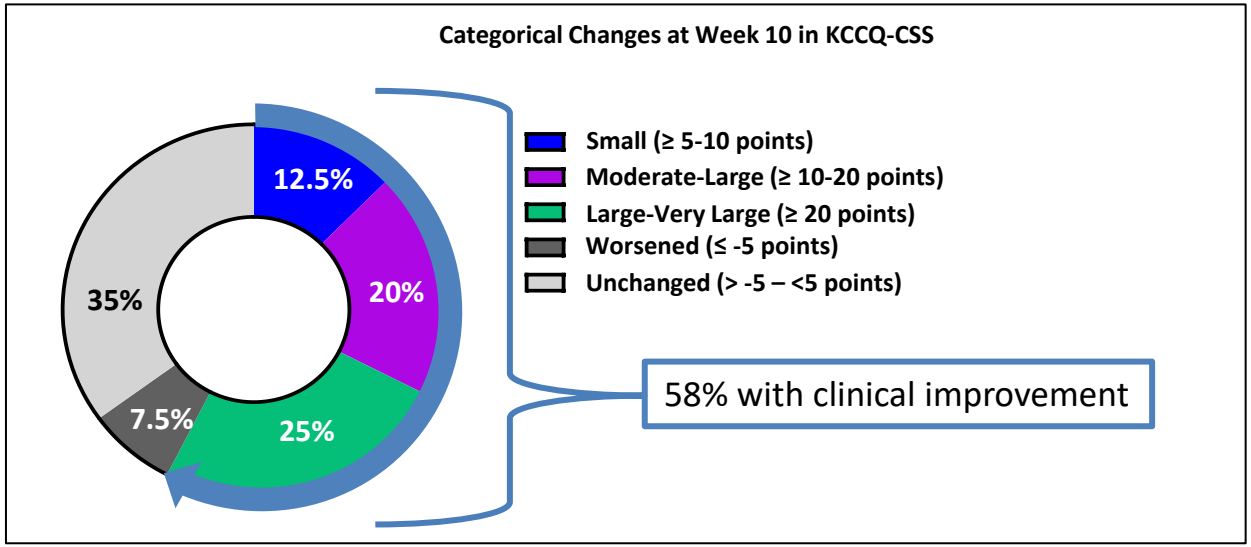
- Modest and reversible reduction in LVEF from baseline to Week 10 of -5.5% (9.9)

- No treatment interruptions or down-titration events related to LVEF < 50% and no events with LVEF < 40%



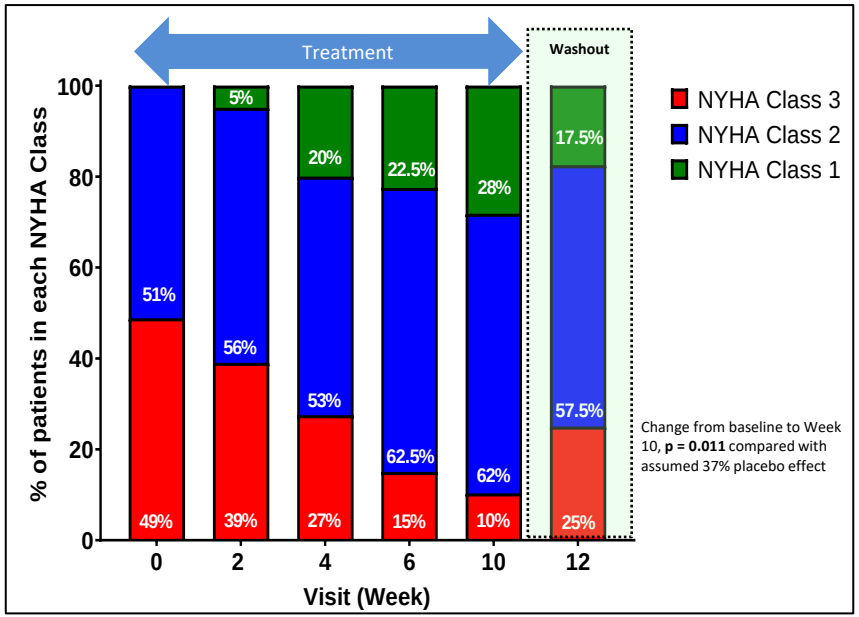
Kansas City Cardiomyopathy Questionnaire



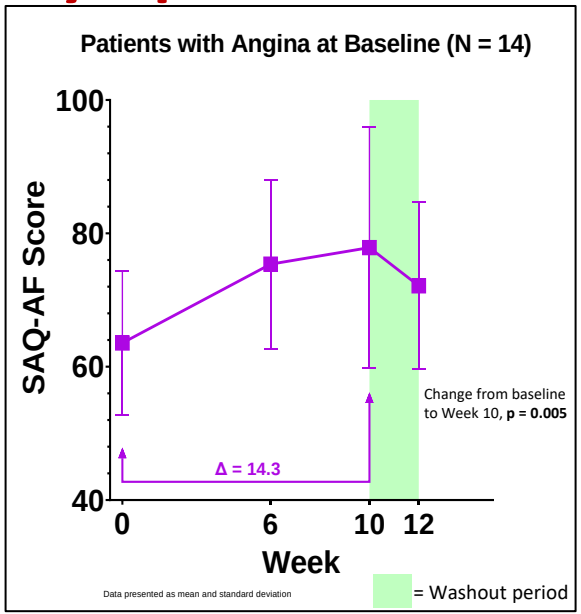


- Mean improvement in KCCQ-CSS of 10.6 points ($p < 0.0001$ for change from baseline to 10 weeks)
- 58% of all patients had clinical reduction in symptom burden, with almost half of the patients reporting moderate to very large improvements

NYHA Functional Class and Angina Symptoms

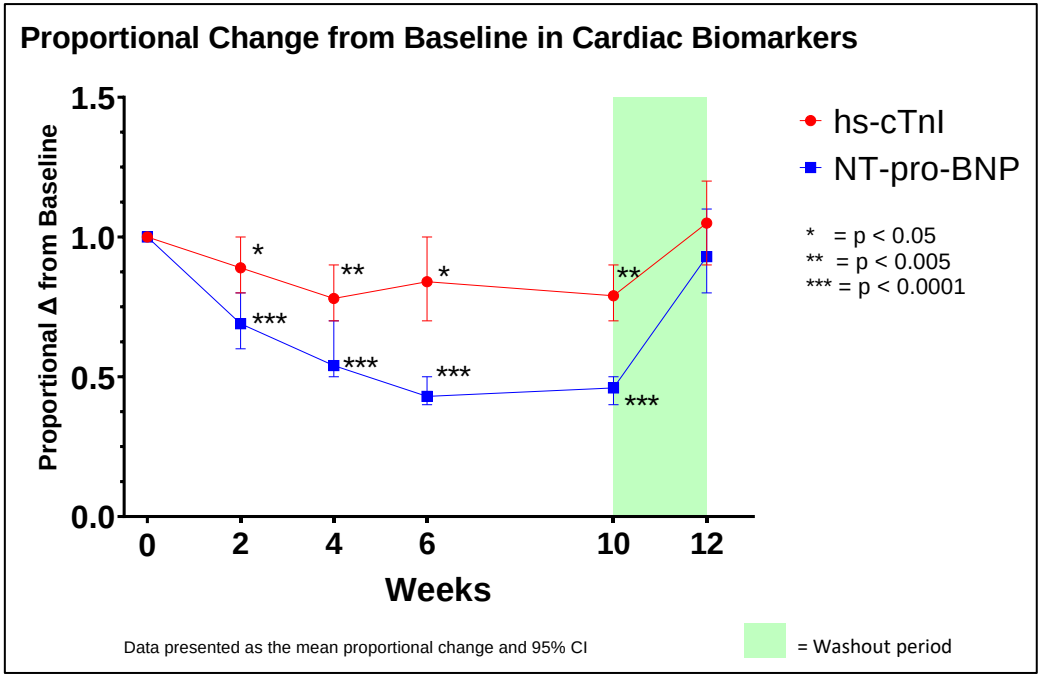


56% of all patients demonstrated functional improvement of ≥ 1 NYHA class and 28% of patients achieved NYHA Class 1 (asymptomatic) by Week 10



Mean reduction in angina frequency score of 14.3 points - translates to a reduction in the frequency of angina from daily or weekly, to weekly or monthly

Cardiac Biomarkers



- Patients were found to have →
  - Mean (SE) relative reduction in **high-sensitivity cardiac Troponin** of 21% by Week 10 with an absolute reduction of -24.8 ng/L (11.6)
  - Mean (SE) relative reduction in **NT-proBNP** of 55% by Week 10 with an absolute reduction of -870 pg/mL (155.3)

Safety

- **LVEF<50%**
  - 3 (7.3%) patients experienced LVEF<50% at Week 10 (EOT). No LVEF <40% occurred
  - All LVEF returned to normal after 2 weeks' washout (Week 12) and there were no associated SAE's

LVEF <50%						
Age (years)	80		54*		77	
Sex	Male		Male		Male	
Atrial Fibrillation	Paroxysmal AF		Permanent AF		Permanent AF	
Clinical and Biomarker Data						
	Baseline	Week 10	Baseline	Week 10	Baseline	Week 10
NYHA Class	II	I	II	II	III	II
KCCQ-CSS	66.2	95.3	100	93.8	90.6	94.8
NT-proBNP (pg/mL)	5755	1707	853	1610	1451	886
Echocardiographic LVEF (Core Lab)						
	Baseline	Week 10	Baseline	Week 10	Baseline	Week 10
LVEF(%)	66	48	72	43	57	41

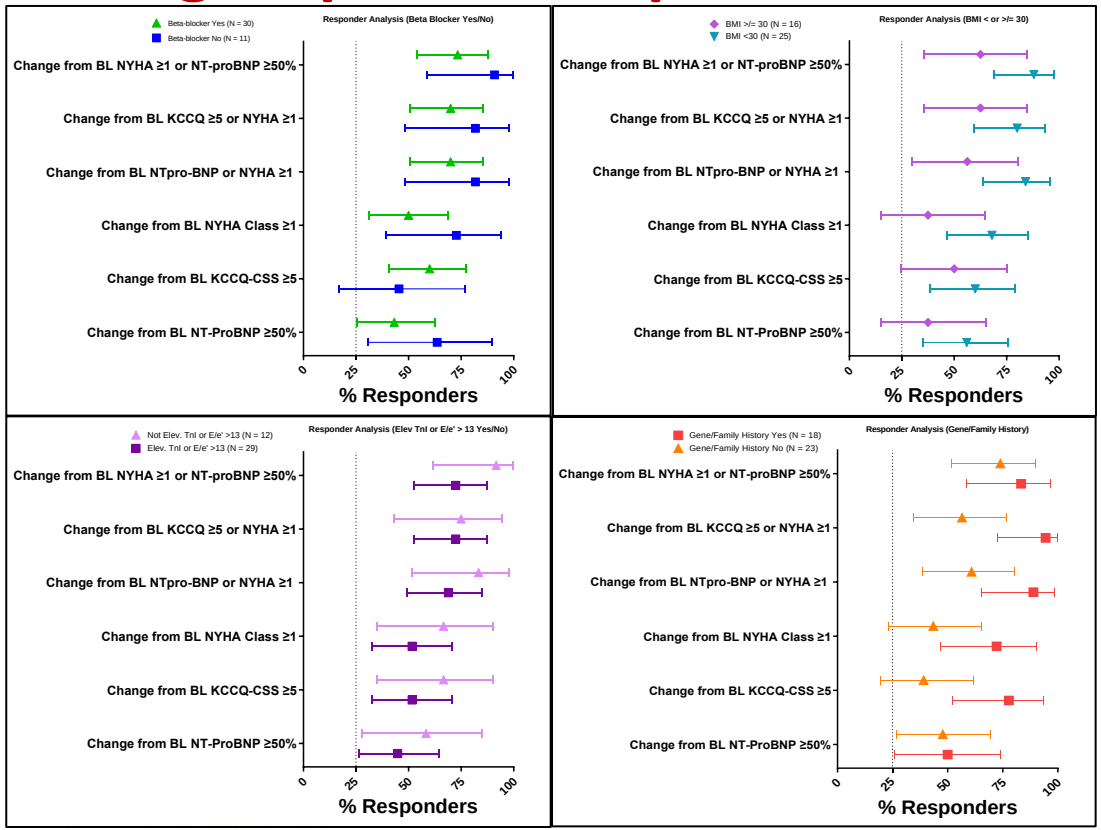
* The patient was experiencing an episode of uncontrolled atrial flutter that required change in treatment (unrelated to *aficamten*)

- **SAEs**
  - 4 (9.8%) patients experienced SAEs including one death. None were attributed to *aficamten*
  - One death in a patient (previously reported) with 2x prior history of aborted sudden cardiac death and an ICD in place

Cardiac Arrest			
Age (years)	43		
Sex	F		
Clinical and Biomarker Data			
	Baseline	Week 6	UNS
NYHA Class	III	II	
KCCQ-CSS	75	86.5	
NT-proBNP (pg/mL)	1103	368	467
hs-cTnI (ng/L)	5.8	<3.5	<3.5
Echocardiographic LVEF (core lab)			
	baseline	Week 6	
LVEF (%)	73.3	75.7	

Exploratory Analyses

Subgroups and Responders

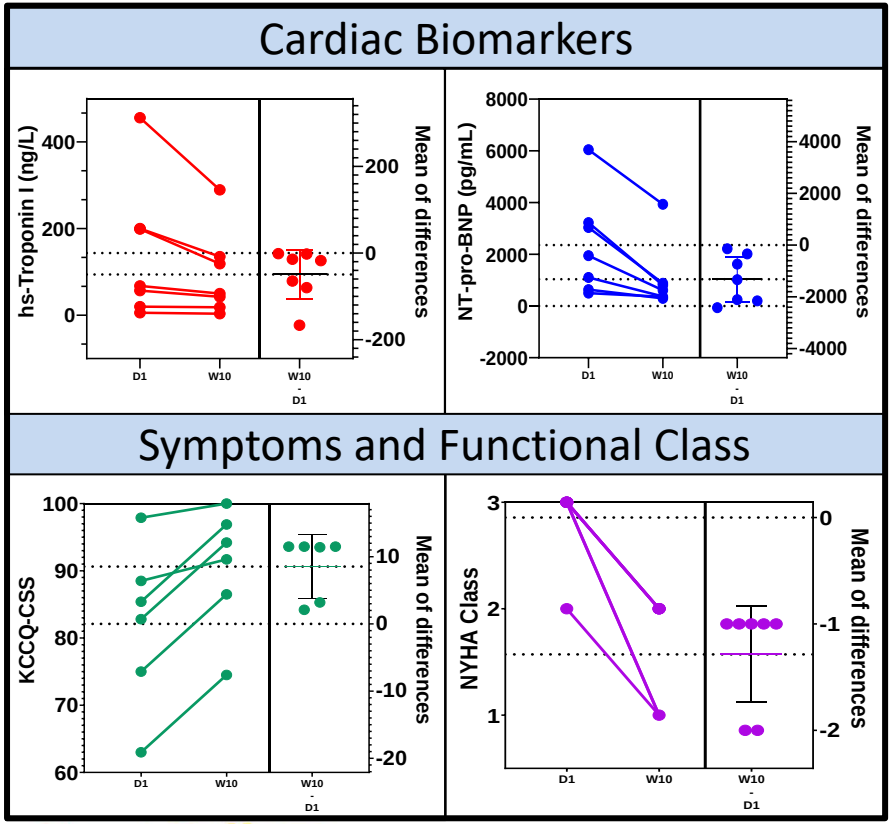


- Responders were defined as either:
  - NT-proBNP reduction ≥ 50%
  - NYHA Class ≥ 1
  - KCCQ ≥ 5 points
  - Combinations of the above

- Subgroup Analyses showed:
  - **Consistent treatment effect across multiple subgroups independent of responder definition**
  - Potential differential treatment effect in obese versus non-obese patients

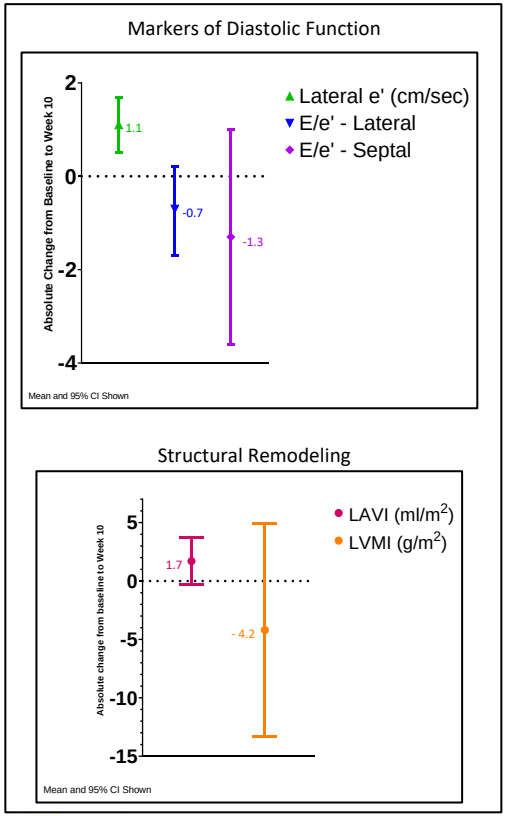
..... = 25% treatment response rate

Patients with Mid-Cavitary Obstruction



- Patients with mid-cavitary obstruction represent a subgroup of nHCM patients, often excluded from other studies, but suffer substantially from limiting symptoms
- 7 patients with mid-cavitary obstruction were studied within REDWOOD-HCM Cohort 4
- All patients in this subgroup showed reduction in both NT-proBNP and hs-Troponin I levels and symptom improvement

Measures of Diastolic Function and Cardiac Structure



- Trends to improvement in Doppler measures of diastolic function
- No statistically significant improvements in structural remodeling during the short treatment duration although trend to reduced LVMI
- These data suggest that longer exposure at target doses may result in favorable remodeling and echocardiographic evidence of improved myocardial relaxation

Data from non-atrial fibrillation patients only (N=37)
E = mitral inflow velocity; e' = mitral annular tissue velocity;
LAVI = left atrial volume index; LVMI = left ventricular mass index

Conclusions

- *Aficamten* treatment was generally well tolerated in patients with nHCM.
- There was a modest and rapidly reversible reduction in LVEF with no LVEF excursions below 40%, and no clinical events of heart failure.
- Most patients reported important improvements in several metrics of health status and functional capacity, with symptom relief being paralleled by reduced plasma cardiac biomarkers.
- Patients who complained of chest pain at baseline reported a significant reduction in the frequency of angina.
- *Aficamten* was broadly effective across several subgroups in the study, including those with mid-cavitary obstruction.
- These results support further study of *aficamten* in the planned Phase 3 trial of nHCM patients.