Efficacy and Safety of *Aficamten* in Patients With Symptomatic Obstructive Hypertrophic Cardiomyopathy

Interim Results From The Randomized Evaluation of Dosing With *Aficamten* (CK-3773274) in Hypertrophic Cardiomyopathy (REDWOOD-HCM) Open Label Extension Study

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Background and Overview

- *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 of patients with oHCM

Cohort	N	Population	*Aficamten* Doses	Design
Cohort 1	21	oHCM	5, 10, 15 mg	Placebo controlled
Cohort 2	20	oHCM	10, 20, 30 mg	Placebo controlled
Cohort 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, improvements in NYHA functional class, and reduction in cardiac biomarkers
- The REDWOOD-HCM Open Label Extension (OLE) is evaluating long-term safety and efficacy of *aficamten* in patients with HCM over a 5-year period

REDWOOD-HCM OLE: Study Design

- Truncated Echo
- 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 clinical PK monitoring

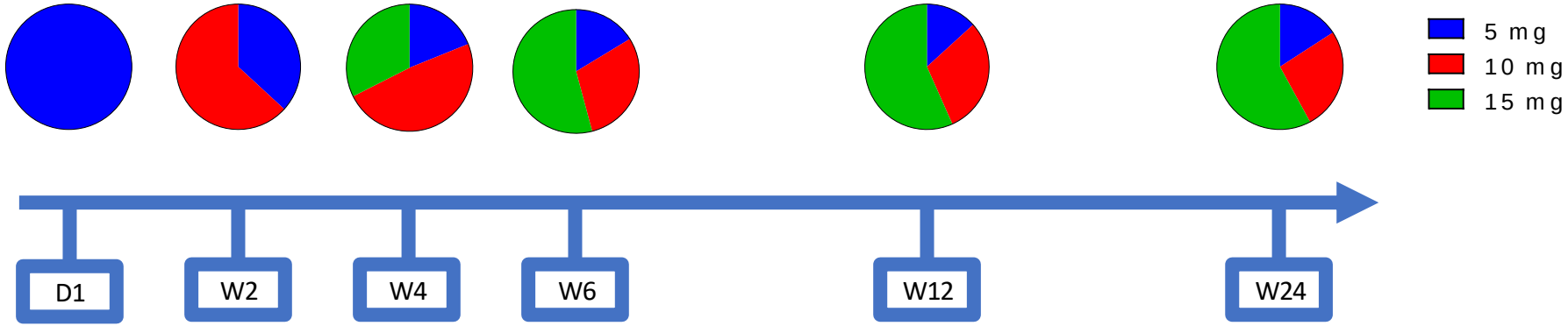
REDWOOD-HCM OLE: Baseline Characteristics

Baseline Characteristics	N = 38
Age (Years), Mean (SD) [Range]	59.9 (13.0) [23 - 82]
Female, n (%)	22 (57.9%)
BMI (kg/m2), Mean (SD) [Range]	30.1 (6.5) [22- 51]
NYHA 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%)**
LVEF* at Screening (%), Mean (SD) [Range]	69.7 (4.1) [60-78]
LVOT-G*, Rest at Screening (mmHg), Mean (SD) [Range]	47.0 (26.6) [10-95]
LVOT-G*, Valsalva at Screening (mmHg), Mean (SD) [Range]	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 in Weeks, Mean (SD) [Range]	**25.7** (11.7) [5-47]

*Site read of screening echocardiogram

REDWOOD-HCM OLE: *Aficamten* Dosing Over Time

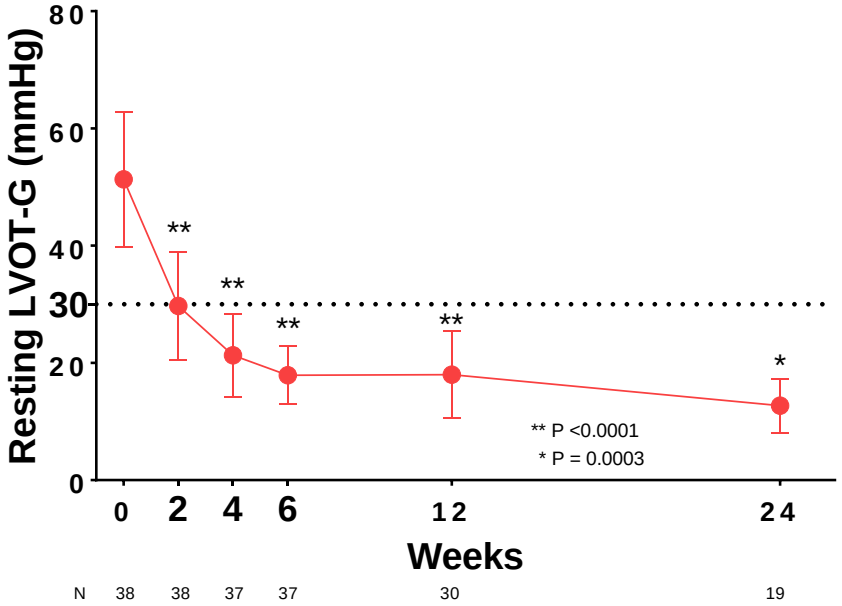
- **Site-read** echo-guided dose titration criteria
  - Up-titration if LVEF ≥ 50% plus at least one of the following
    - Resting LVOT-G ≥ 30 mmHg
    - Valsalva LVOT-G ≥ 50 mmHg
  - Down-titration if LVEF < 50%
  - Interruption if LVEF < 40%



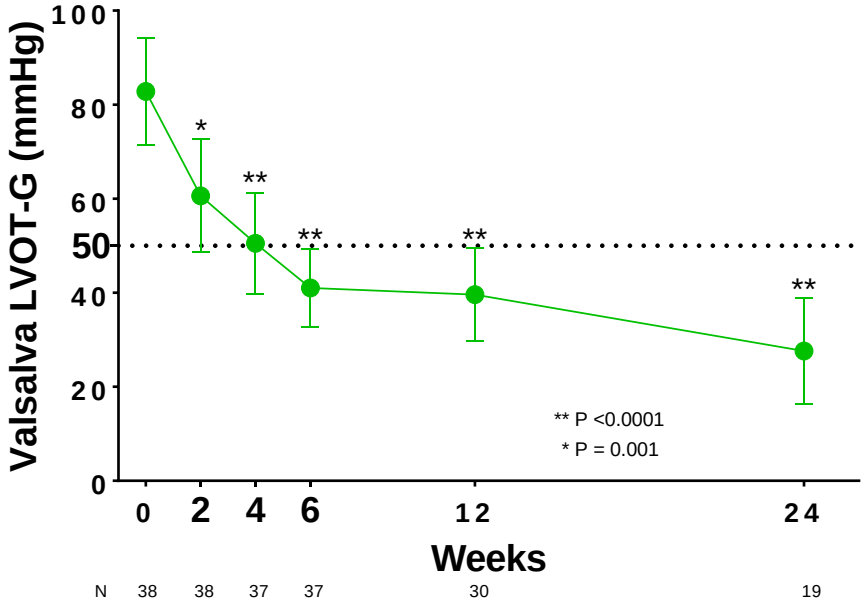
Rapid and Sustained Reduction in LVOT Gradient

REDWOOD HCM OLE

Resting LVOT Gradient



Valsalva LVOT Gradient

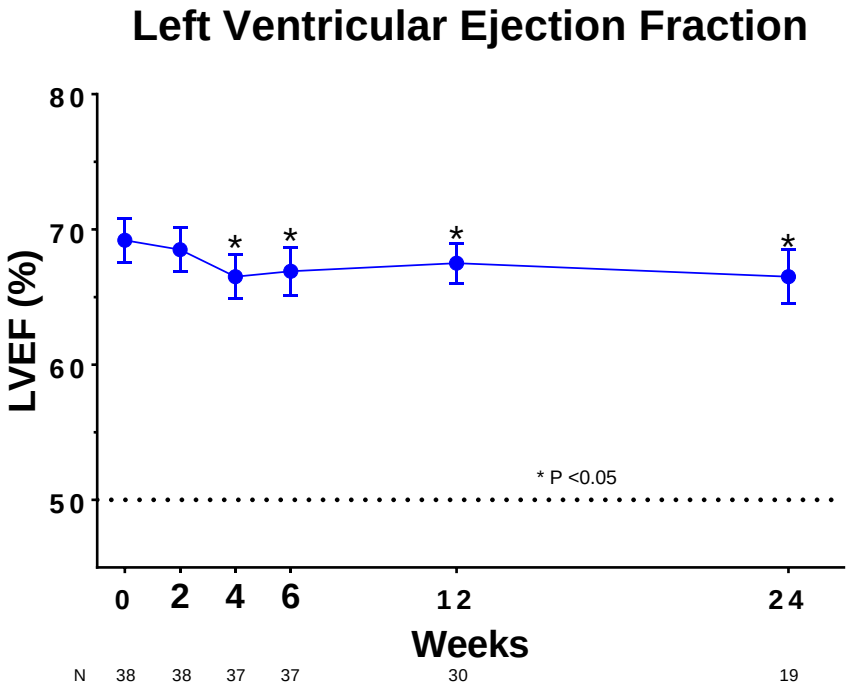


Data presented as mean ± 95% Confidence Interval

Echocardiographic data from site reads

Minimal and Stable Reduction in LVEF

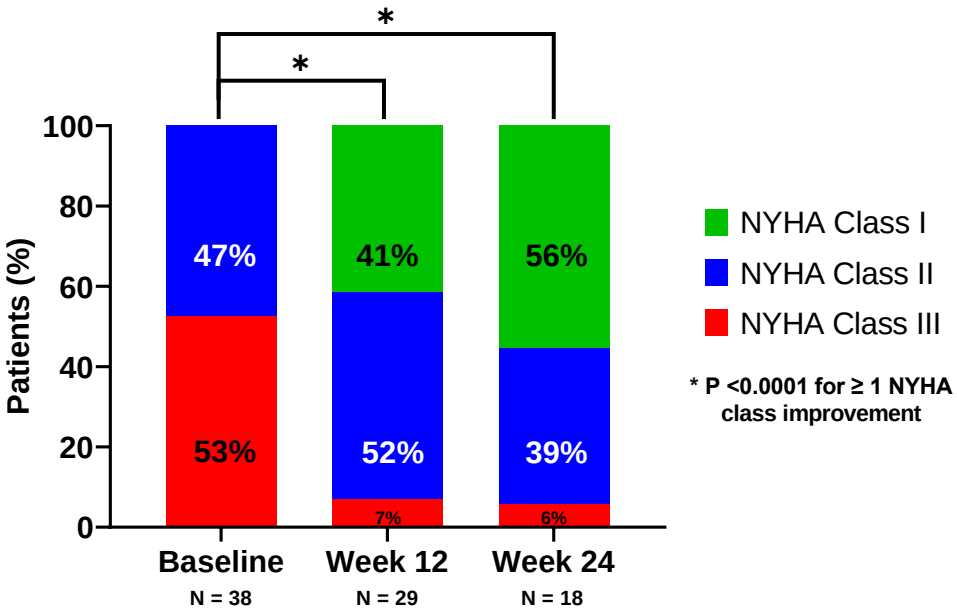
REDWOOD HCM OLE

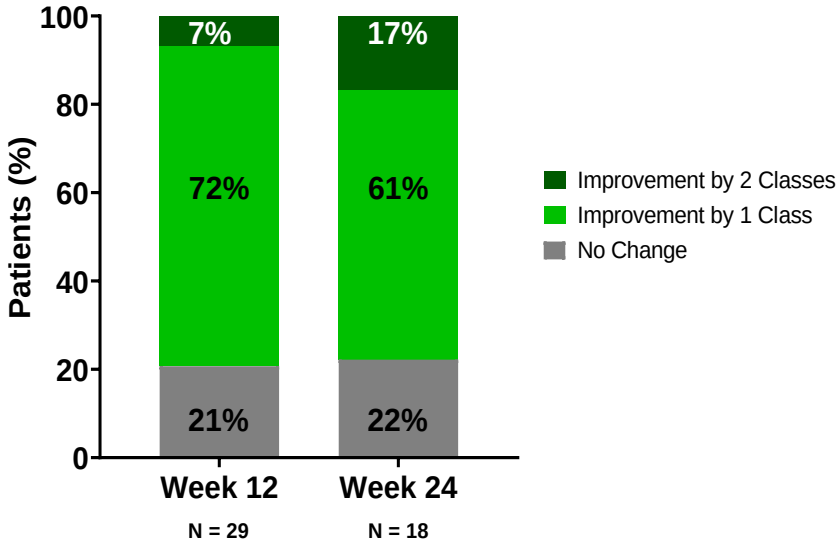


Data presented as mean ± 95% Confidence Interval

Echocardiographic data from site reads

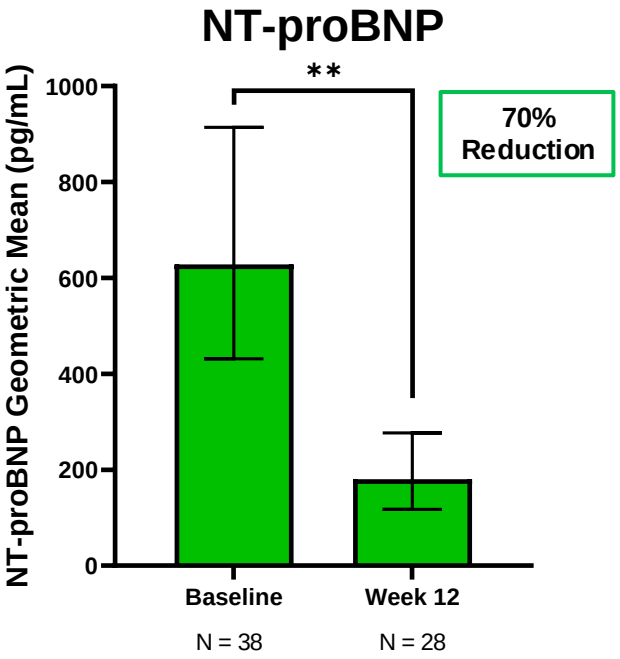
Improvement in NYHA Class

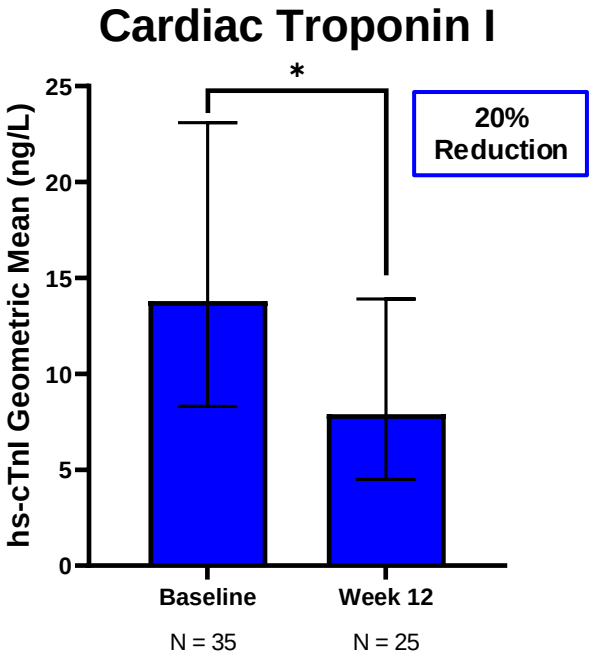




No patients had a worsening of NYHA class from baseline

Decrease in Cardiac Biomarkers





** p < 0.0001 for proportional change from baseline

* p = 0.002 for proportional change from baseline

Data presented as geometric mean ± 95% Confidence Interval

REDWOOD-HCM OLE: Safety

	N=38
Patients with at Least One TEAE	28 (74%)
Patients with at Least One Related TEAE	8 (21%)
Patients with at Least One TESAE	2 (5%)
Patients with at Least One Severe TEAE	1 (3%)
Patients with TEAE Leading to Drug Interruption	1 (3%)
Patients with TEAE Leading to Dose Reduction	2 (5%)

TEAE: Treatment Emergent Adverse Event
TESAE: Treatment Emergent Serious Adverse Event

AEs occurring in more than 1 subject

- Headache (4)
- Dizziness (3)
- Alopecia (2)
- Atrial fibrillation (2)
- Diarrhea (2)
- Fatigue (2)
- Parosmia (2)
- Rash (2)
- Sinusitis (2)

REDWOOD-HCM OLE: Safety

Subject 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 **restarted *aficamten* at 5 mg**

Subject with temporary down-titration

Investigator was concerned about QTc prolongation in a subject with abnormal baseline EKG

- → **Temporary *aficamten* down-titration** pending core-lab QTc interpretation
- → Confirmed that the QTc was normal, and *aficamten* was subsequently increased

Subject 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

Summary and Conclusions

REDWOOD HCM OLE

- In this open label extension study of patients with obstructive HCM treated with background medical therapy including *disopyramide*, *aficamten* was associated with:
  - **Significant and sustained reductions in LVOT gradients**
  - **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 that the treatment effect of *aficamten* is durable for up-to 6 months
- SEQUOIA-HCM is an ongoing pivotal Phase 3 trial of *aficamten* in patients with obstructive HCM