HFSA 2021

ANNUAL SCIENTIFIC MEETING

WHERE **HEART FAILURE TEAMS** GATHER

SEPT 10-13 + Denver, CO + Virtual

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REDWOOD HCM

Randomized **E**valuation of **D**osing **W**ith *Aficamten* in **O**bstructive **O**utflow **D**isease - **HCM**

Results from Cohorts 1 & 2

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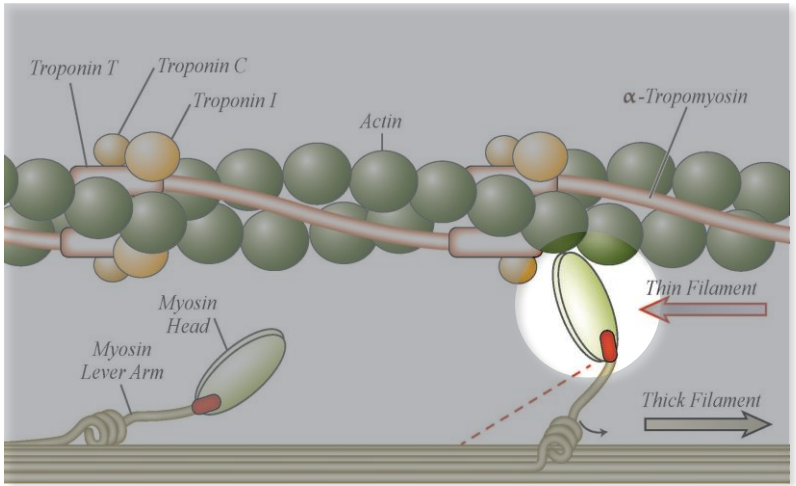
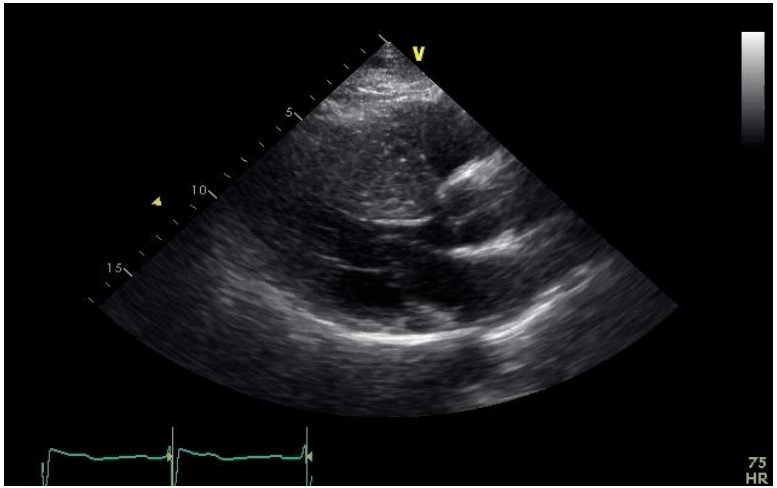
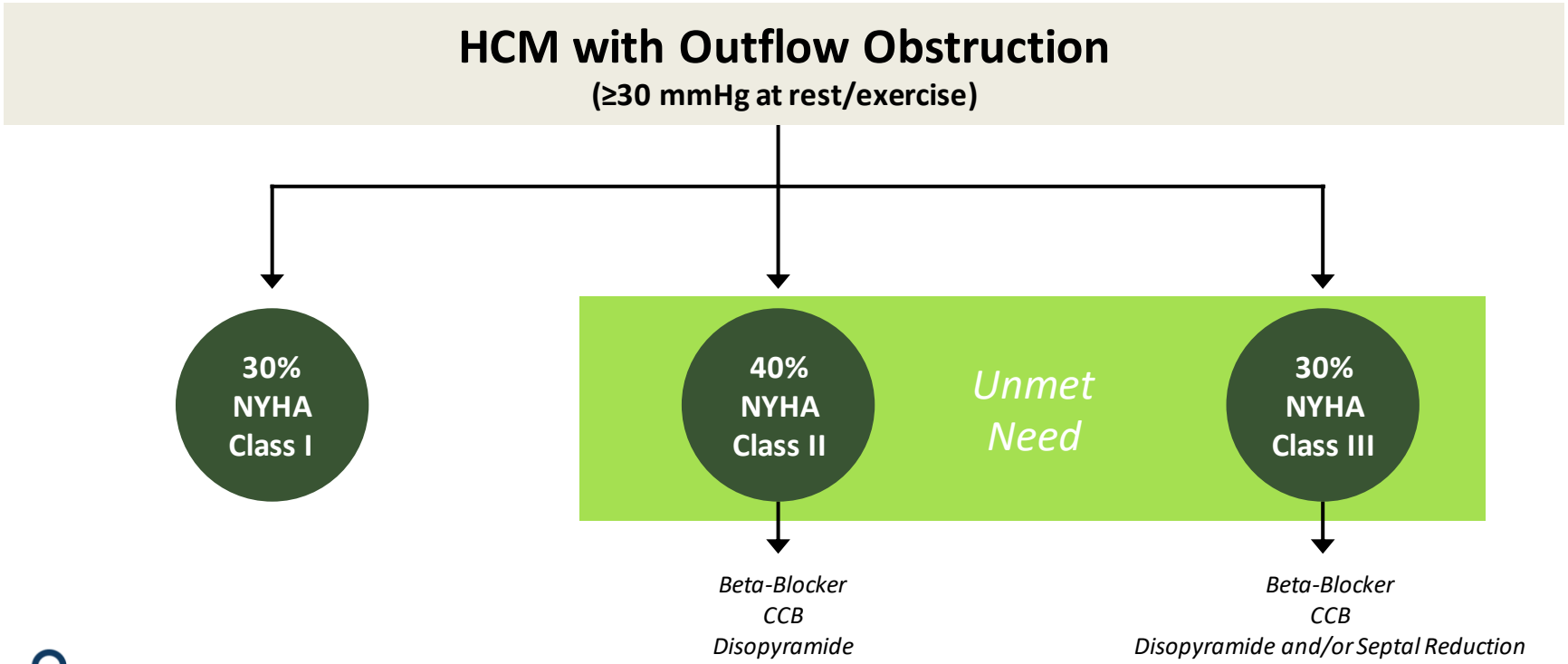
Hypertrophic Cardiomyopathy (HCM)

- HCM is characterized by hypercontractility of the left ventricle - a major contributor to the mechanism of LV outflow tract (LVOT) obstruction and the generation of a pressure gradient between the LV cavity and the systemic circulation
- Outflow tract obstruction is a strong and independent predictor of heart failure symptoms
- *Aficamten* is a small molecule ***selective cardiac myosin inhibitor*** - targeting the mechanism of hypercontractility in HCM, in an effort to decrease or abolish LVOT gradients (LVOT-G) and substantially improve heart failure symptoms





The *Unmet* Treatment Need in *Obstructive* HCM



Aficamten - Key Pharmacological Features

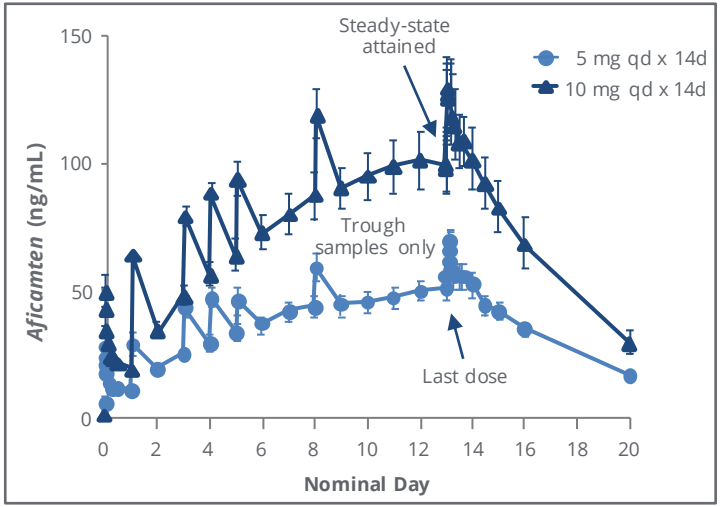
- **Optimized plasma half-life → 3.4 days**
  - Once daily dosing
  - Steady-state achieved by 2 weeks allowing rapid dose adjustments
  - Rapid reversibility

- **Shallow exposure-response relationship**
  - Wide therapeutic window
  - Enables individualized pharmacodynamically guided dose adjustment
  - No need for PK-guided dosing

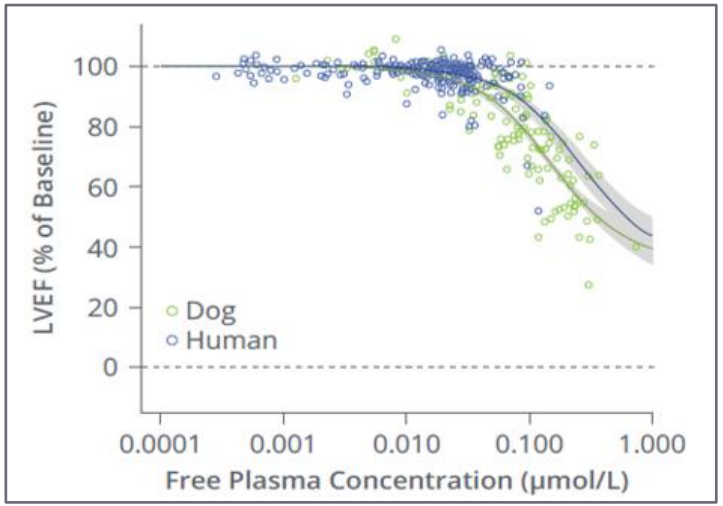
- **Minimal drug-drug interactions → No significant CYP inhibition or induction.**

Aficamten - Dosing & PK/PD Relationship (Ph 1)

Steady-State Achieved After 14 Days of Dosing



PK/PD Relationship of *Aficamten* for LVEF



Shallow Exposure-Response Relationship and Steady State at 2 Weeks in Humans Informed the Broad Dose Range and Short Titration Schedule Studied in REDWOOD-HCM

REDWOOD-HCM - Key Inclusion Criteria and Endpoints

Study Design and Endpoints

- Randomized and blinded dose finding study
  - 2 Cohorts exploring 5 overlapping doses (5mg to 30 mg)
  - Evaluating:
    - Safety and Tolerability
    - Resting and Valsalva LVOT gradient
    - Change in LVEF
    - NYHA class
    - NT-proBNP

Key Inclusion Criteria

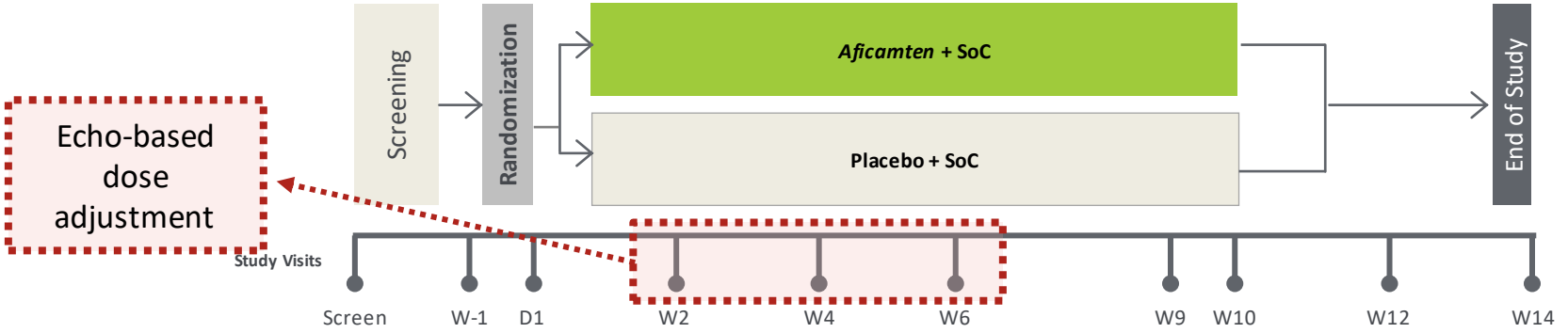
- 18-85 years old
- LV wall thickness of ≥15 mm
- Symptomatic (NYHA FC II-III) Obstructive HCM
  - Resting LVOT-G ≥ 50 mmHg

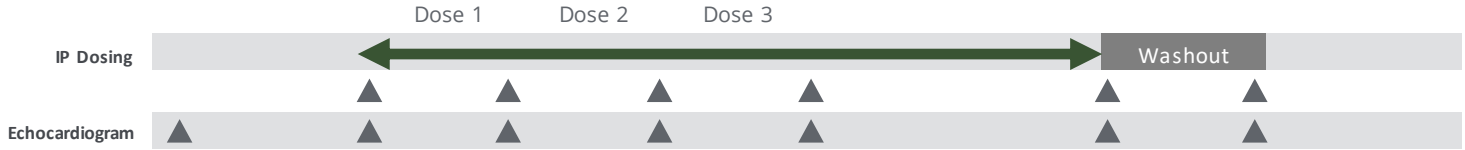
    OR
  - Resting LVOT-G ≥ 30 mmHg AND Valsalva LVOT-G ≥ 50 mmHg
- Baseline LVEF ≥ 60%
- Stable doses of background medical therapy (β-blockers, calcium channel blockers)

LVOT-G = Left ventricular outflow tract gradient

REDWOOD-HCM - Clinical Trial Design

Two sequential and overlapping dose-finding cohorts





	Dose 1	Dose 2	Dose 3
Cohort 1 (n=21)	5 mg	10 mg	15 mg
Cohort 2 (n=20)	10 mg	20 mg	30 mg

REDWOOD-HCM – Baseline Characteristics

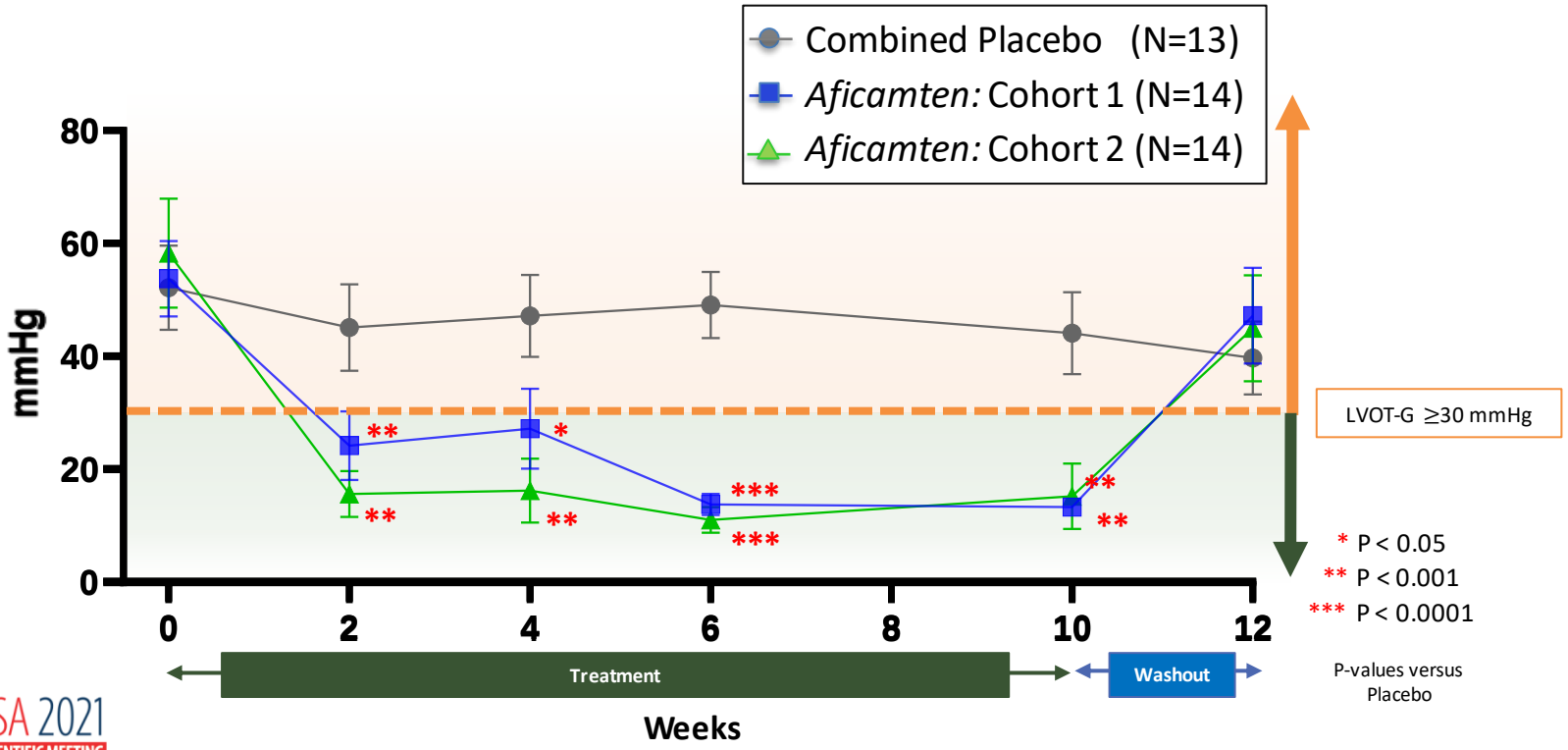
Patient Demographics and Baseline Characteristics (Pooled)

Characteristic	Placebo (n = 13)	*Aficamten* (n = 28)
Age (Years), Mean (SD) [Range]	57.2 (9.6) [36,69]	56.6 (13.6) [33,78]
< 65 Years	10 (77%)	17 (61%)
Sex, n (%)		
Female	8 (62%)	15 (54%)
Race = White, n (%)	12 (92%)	28 (100%)
NYHA Class, n (%)		
Class II	11 (85%)	17 (61%)
Class III	2 (15%)	11 (39%)
Maximal LV Wall Thickness (mm) Mean (SD)	16 (3)	17 (3)
LVEF* at Screening (%), Mean (SD)	73.6 (5.9)	71.7 (8.0)
LVOT-G*, Rest at Screening (mmHg), Mean (SD)	70.0 (28.0)	61.1 (29.8)
LVOT-G*, Valsalva at Screening (mmHg), Mean (SD)	93.3 (27.2)	89.3 (31.5)

* Site-read echocardiogram

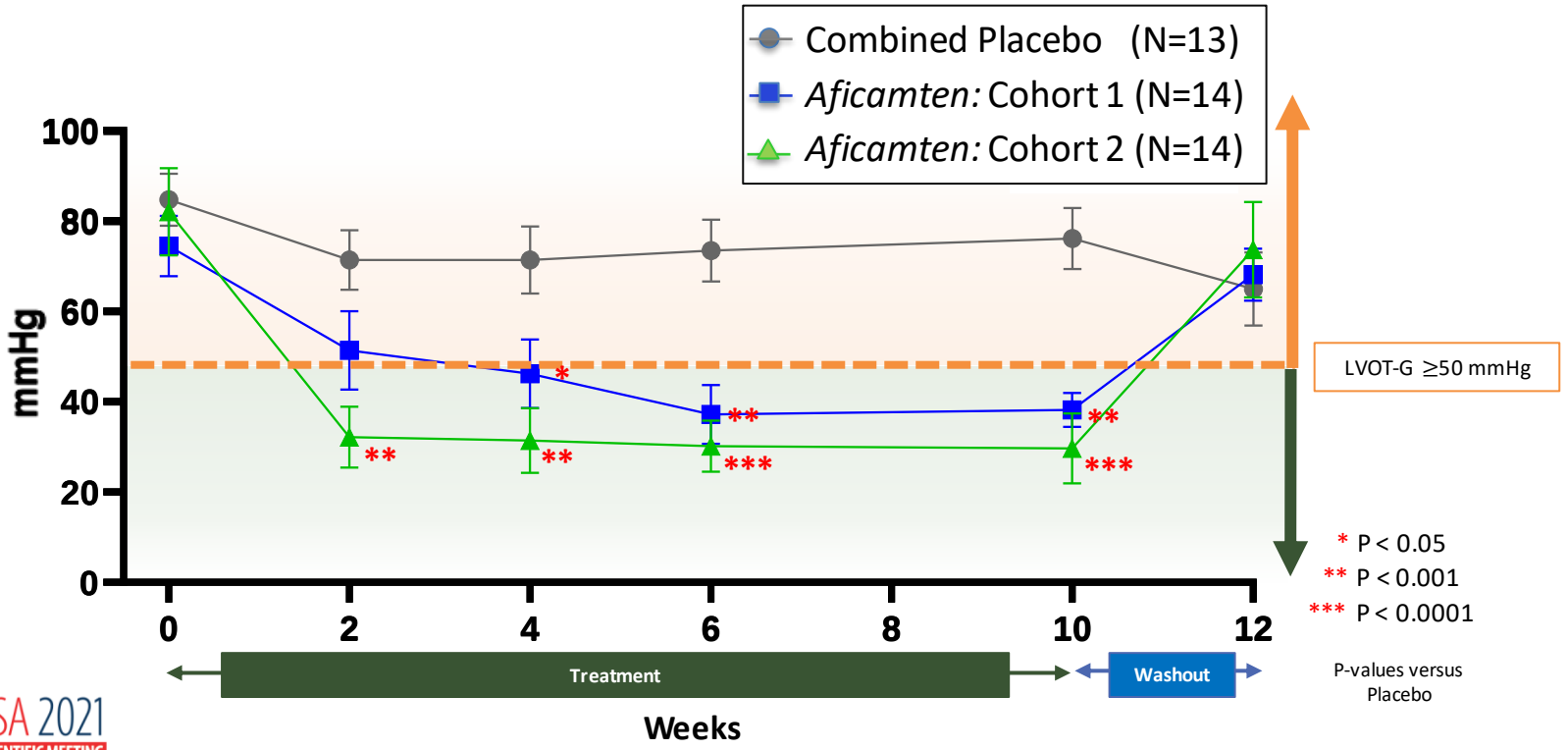
REDWOOD-HCM – Efficacy

Resting Left Ventricular Outflow Tract Gradient (LVOT-G)



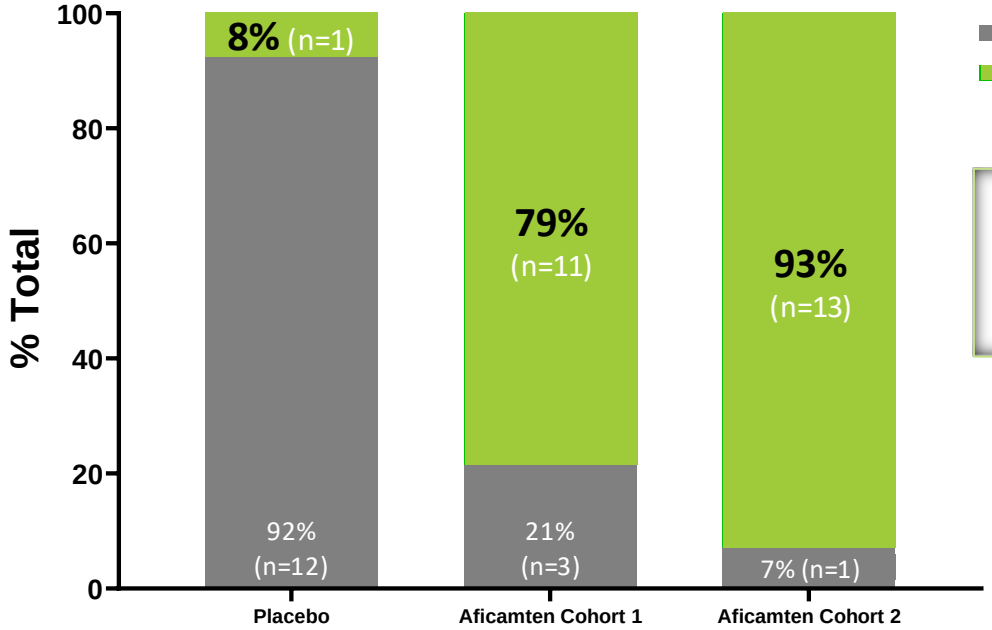
REDWOOD-HCM – Efficacy

Valsalva LVOT-G



REDWOOD-HCM – Efficacy

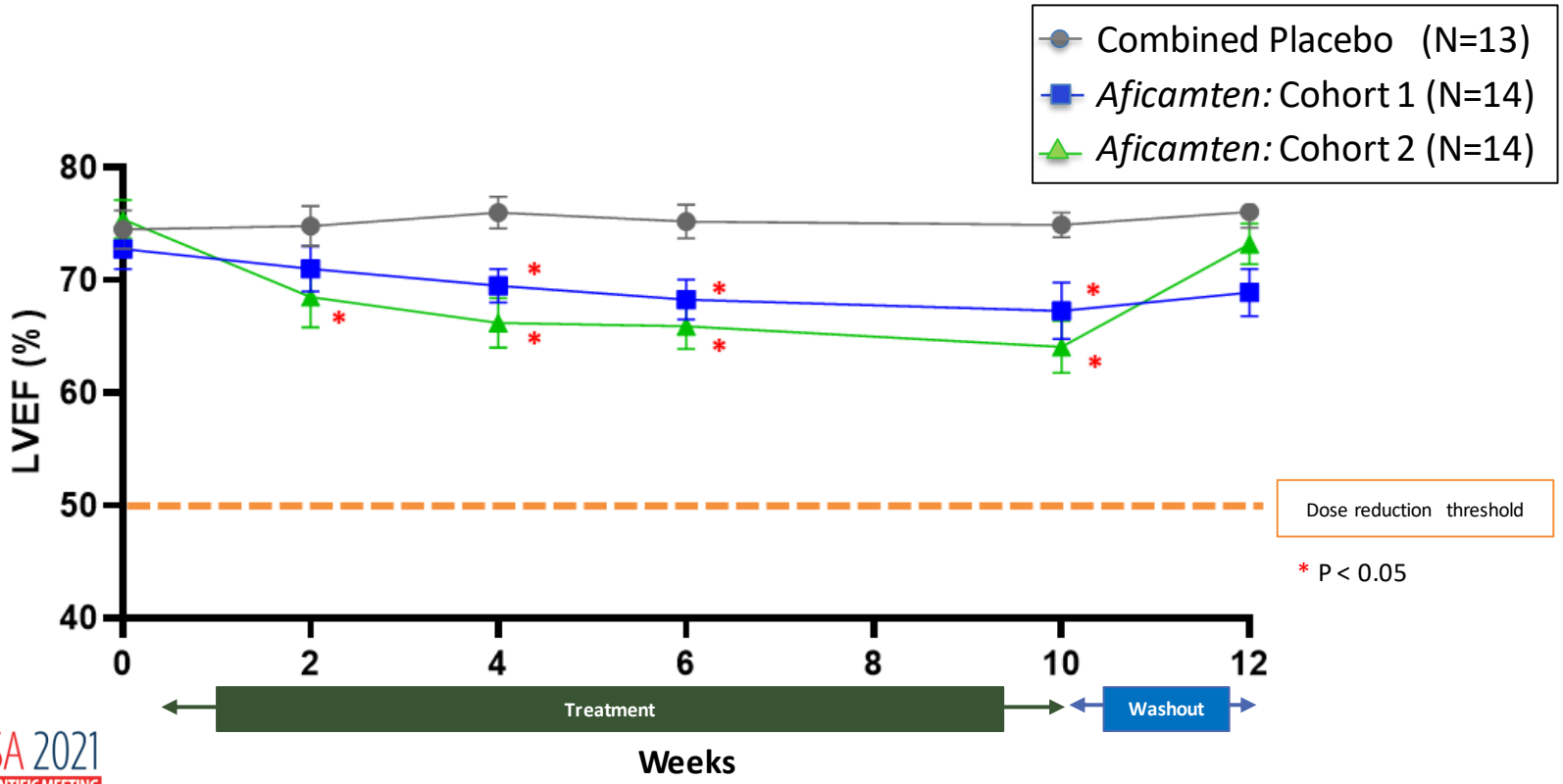
LVOT-G Response Rates on *Aficamten*



Week 10 Responder Definition:
Resting LVOT-G <30 mmHg
and
Valsalva LVOT-G <50 mmHg

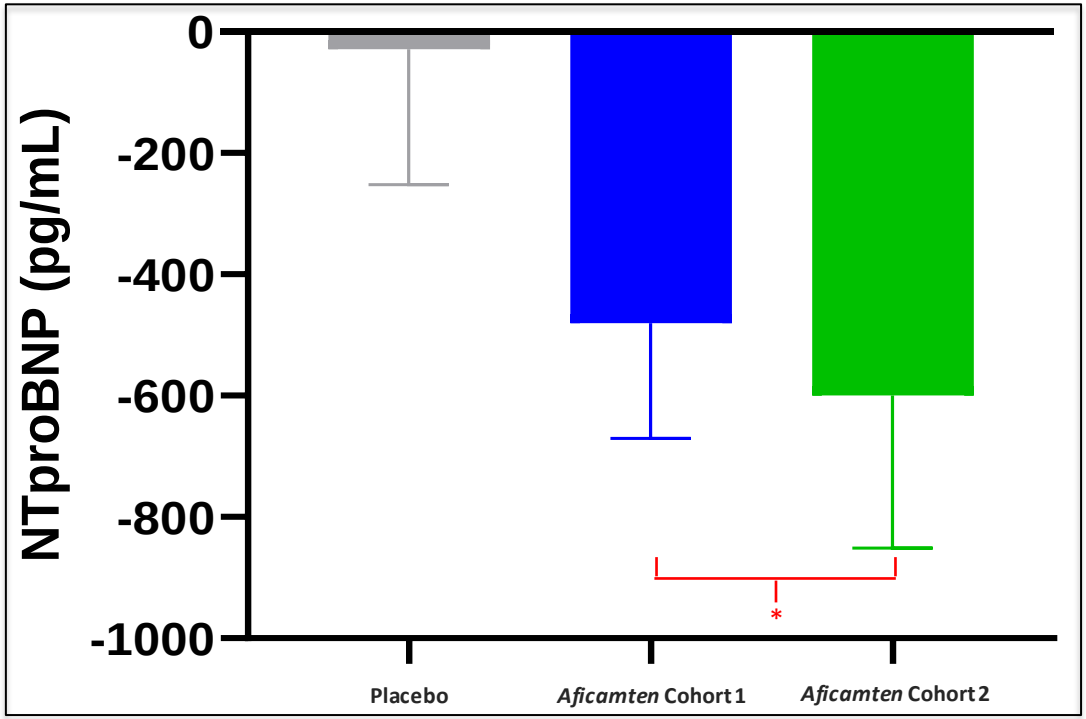
REDWOOD-HCM – Efficacy

Changes in Left Ventricular Ejection Fraction over Study Period



REDWOOD-HCM – Efficacy

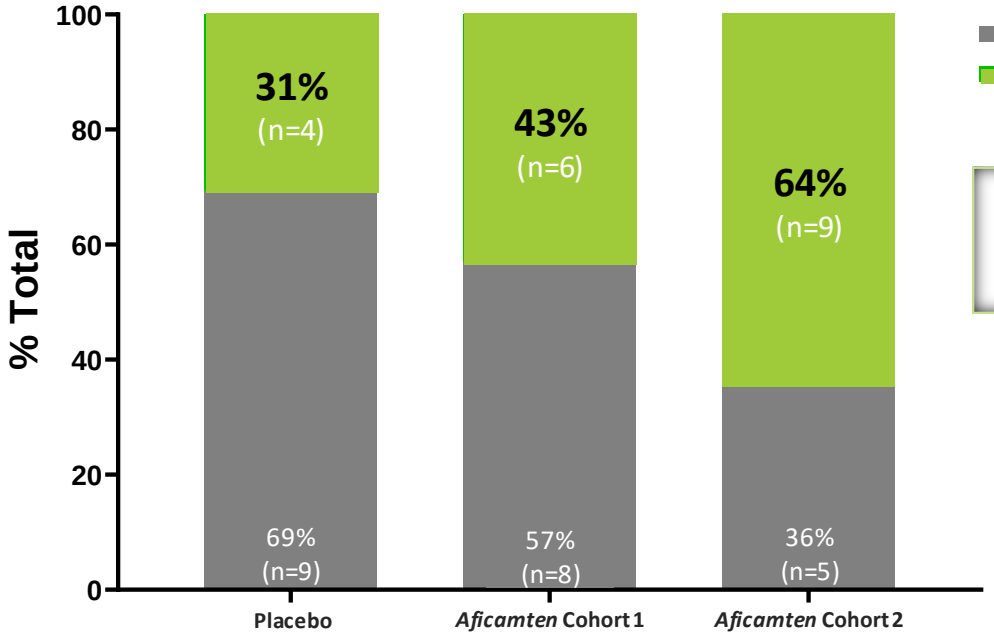
Change from Baseline NT-proBNP to Week 10



* P= 0.003 for Pooled Cohort 1 and 2 versus Placebo

REDWOOD-HCM – Efficacy

Improvement in Heart Failure Symptoms (NYHA Class) on *Aficamten*



Week 10 Responder Definition:

Improvement in NYHA Class ≥ 1

Cohort 1 vs Placebo: p > 0.1
Cohort 2 vs Placebo: p = 0.08

REDWOOD-HCM - Safety

- 2 Serious Adverse Events reported in Cohort 1 and none in Cohort 2

Stress Cardiomyopathy
55-year-old female assigned to **Placebo**, with associated cardiogenic shock after IP discontinuation at end of treatment (Week 10).

Back Pain
50-year-old male assigned to ***aficamten*** (dose 5 mg at the time of SAE, and max dose 15 mg) visited Emergency Room for exacerbation of preexisting musculoskeletal back pain.

- No SAEs reported that resulted in early termination
- No treatment-related serious adverse events
- No imbalance in adverse events between *aficamten* and placebo treated arms

REDWOOD-HCM - Safety

- **No patients met the "stopping criteria" of LVEF < 40%**
- **No treatment interruptions or discontinuations**
- **Treatment Emergent Adverse Events**
  - Placebo 85% of participants
  - *Aficamten* 88% of participants
- **LVEF < 50% (Cohort 2 only)**
  - 1 patient (baseline EF = 58%) underwent per-protocol dose reduction at Week 4 and had LVEF return above 50% (max dose 20 mg)
  - 1 patient (baseline EF = 70%) had LVEF 49.3% at Week 10 (max dose 20 mg; no dose changes) and LVEF returned to baseline at the end of study (Week 12)

REDWOOD-HCM - Summary

- ***Aficamten*** is a **novel second-generation selective cardiac myosin inhibitor** being evaluated as oral drug therapy to treat heart failure symptoms and improve functional capacity in patients with due to obstructive HCM.
- In this **phase II clinical trial** of symptomatic obstructive HCM patients, 10- week treatment with *aficamten* resulted in **elimination of resting LV outflow tract gradients in nearly all patients**, including 93% in higher dose cohort. Improvements in hemodynamics were **mirrored by reductions in NT-proBNP**.
- This **reduction of outflow gradient** was associated with a **substantial improvement in heart failure symptoms** with a substantial proportion of patients achieving one or more improvement in NYHA class.
- The **half-life and wide therapeutic window of *aficamten* enabled**:
  - **Rapid and substantial reduction of the LVOT-G**
  - **Precise echo-guided titration of the drug** without the need for any treatment interruptions
  - **Rapid reversibility** after discontinuation
- ***Aficamten* was well-tolerated**, with no serious adverse events due to the drug and a similar incidence of AEs compared with placebo. No patient discontinued use of *aficamten* during the study period.
- These data strongly support investigating the clinical efficacy and safety of *aficamten* in a larger prospective Phase III clinical trial in obstructive HCM planned to start before year end.