ACC.23: REDWOOD-HCM Cohort 4 & FOREST-HCM

March 6, 2023

Today's Presenters

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SVP, Corporate Communications & Investor Relations

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

ACC2023 Poster Session: 05 March 2023.

Ahmad Masri, MD MS

Cytokinetics

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

Ahmad Masri,[1] Mark V. Sherrid, Lubna Choudhury, Florian Rader, Christopher M. Kramer, Sara Saberi, Timothy C. Wong, Aslan T. Turer, Sherif F. Nagueh, Anjali Tiku Owens, Caroline J. Coats, Iacopo Olivotto, Hugh C. Watkins, Michael A. Fifer, Scott D. Solomon, Theodore P. Abraham, Stephen B. Heitner, Daniel Jacoby, Stuart Kupfer, Fady I. Malik, Lisa Meng, Regina L. Sohn, Amy Wohltman, Martin S. Maron

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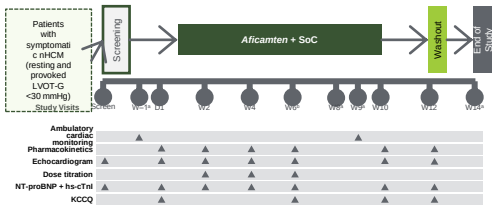
BACKGROUND

- 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

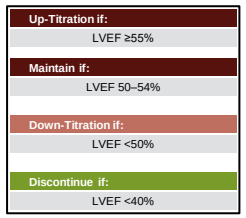


TABLE 1 – Baseline Characteristics

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

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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New Orleans, LA | March 4–6, 2023

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For more information, email masria@ohsu.edu

The REDWOOD-HCM study (NCT04219826) was sponsored by Cytokinetics, Incorporated.

Assistance with formatting this poster was provided by Engage Scientific Solutions, Horsham, UK, and was funded by Cytokinetics, Incorporated.

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]
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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.
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FIGURE 3

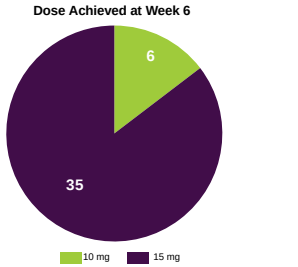

Figure 3: 35 patients (85%) achieved daily *aficamten* dose of 15 mg; 6 patients (15%) achieved 10 mg; 1 patient on 10 mg did not complete the titration period because *aficamten* was discontinued due to personal reasons.

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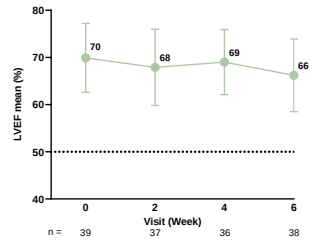

Figure 4: LVEF mean (SD) core lab assessments during titration period. Although LVEF decreased modestly, no LVEF was <50% during this period.

FIGURE 5

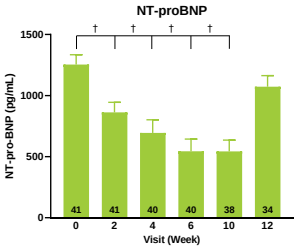

Figure 5: Geometric mean NT-proBNP (%CV) decreased at each scheduled visit with the proportional change from baseline being highly statistically significant († P<0.0001).

FIGURE 6

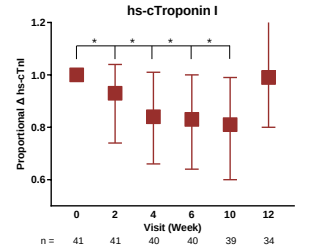

Figure 6: hs-cTnI decreased significantly at each study visit compared to baseline (* P<0.05). After the 2-week washout, cardiac biomarkers returned to baseline.

FIGURE 7

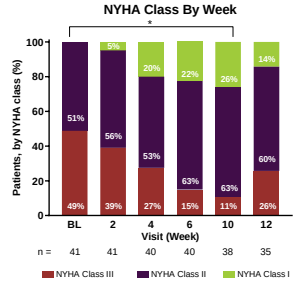

Figure 7: NYHA class improved during treatment (* P<0.05): 22 of 41 (54%) patients experienced a change of ≥1 NYHA class, including 12 patients who improved from class III to II; 2 patients improved from class III to I; and 8 from class II to I.

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.

Cytokinetics

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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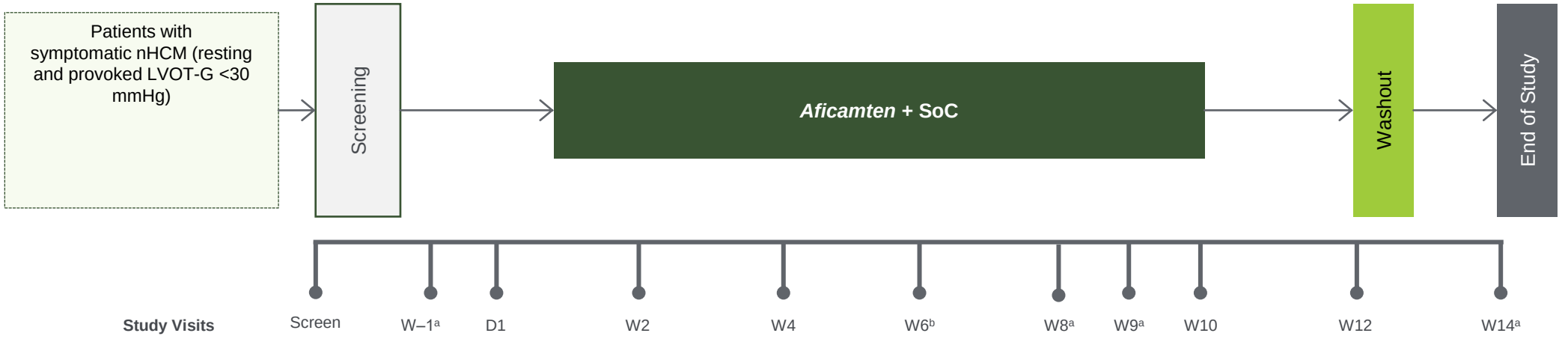

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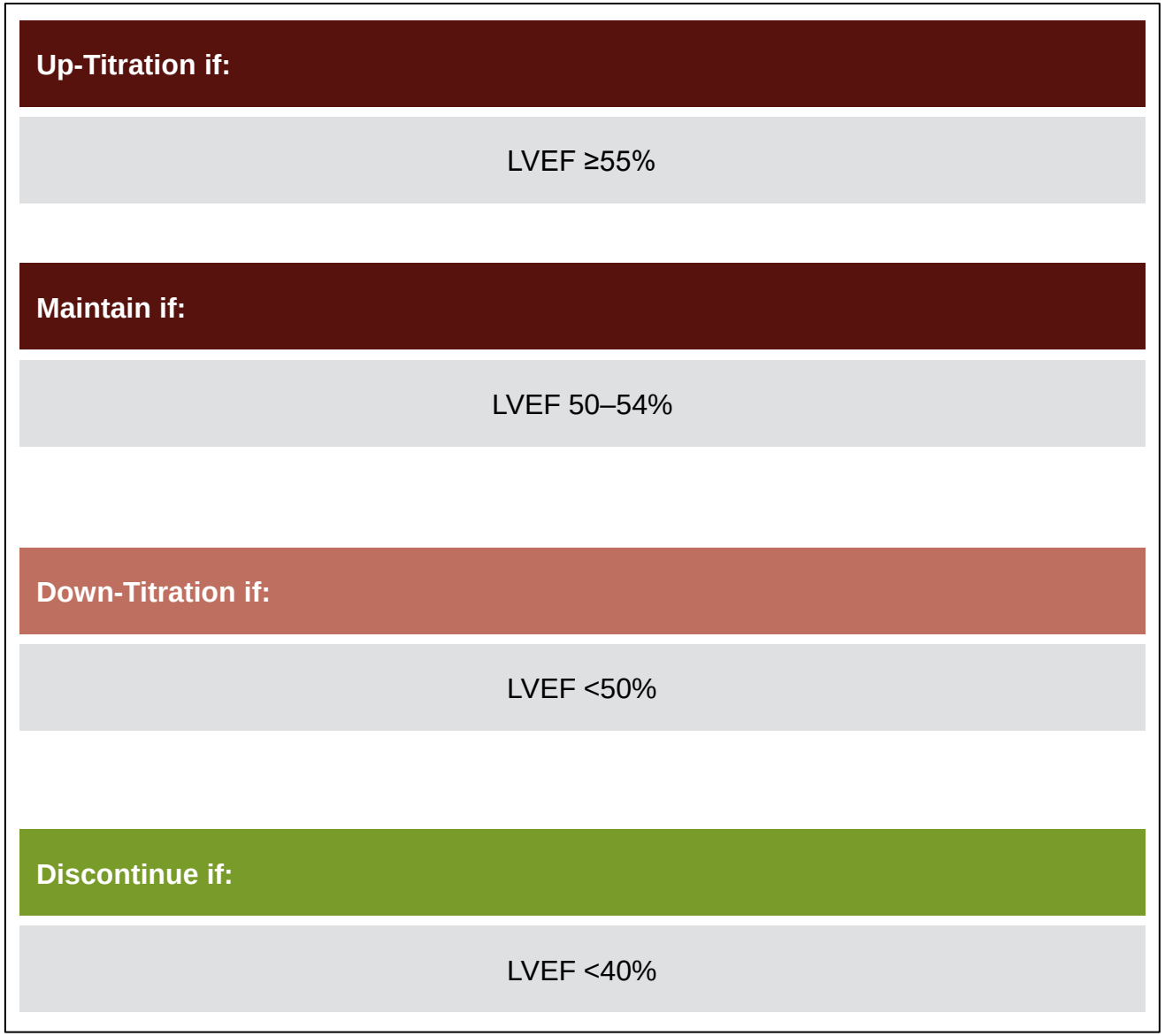

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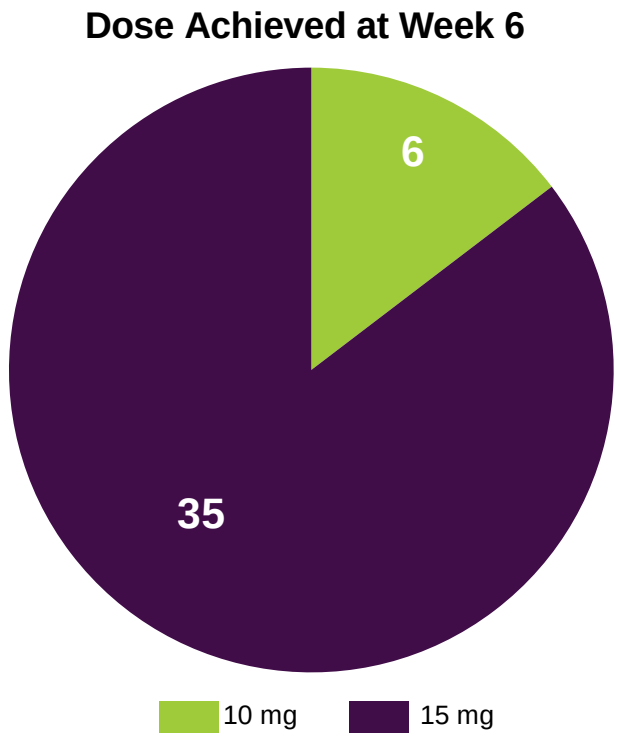

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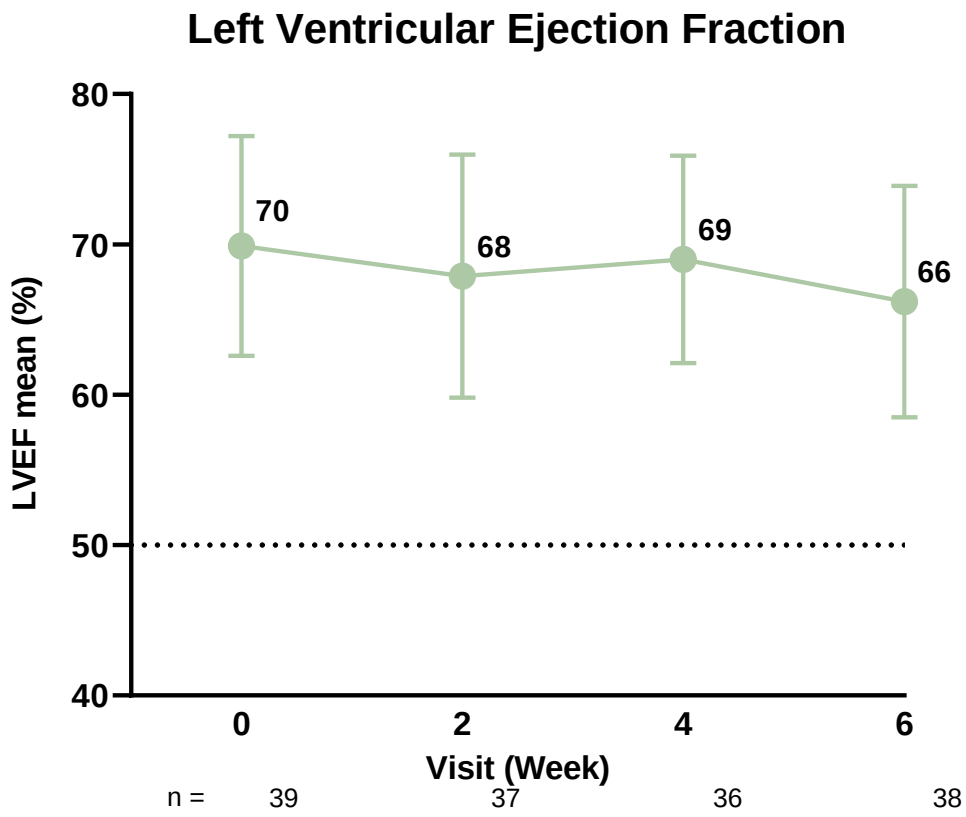
Figure 4: Left Ventricular Ejection Fraction (Titration Period)



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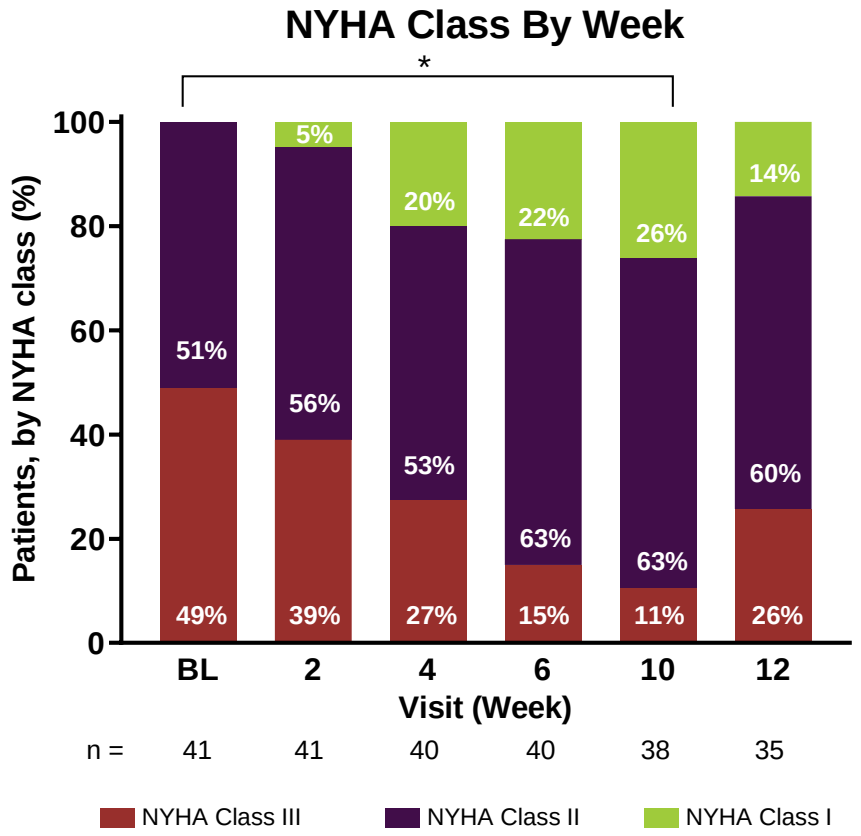
Change in NYHA Class



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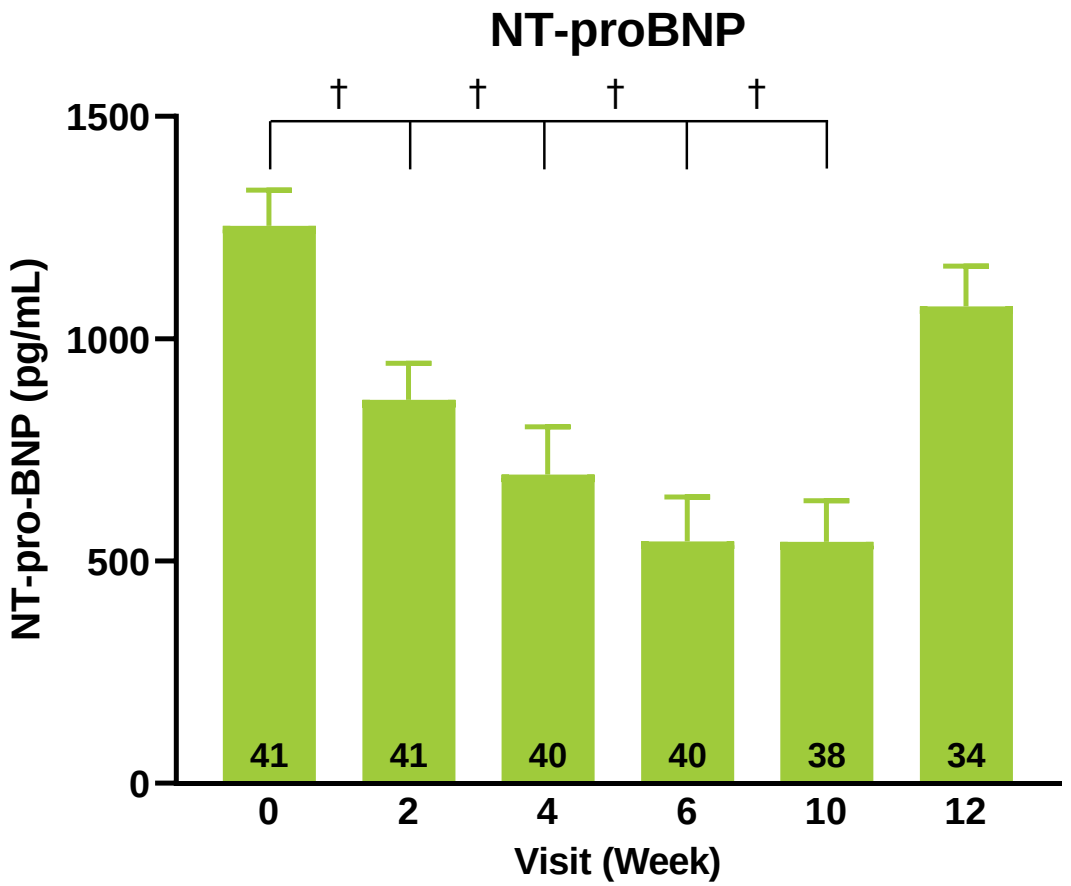

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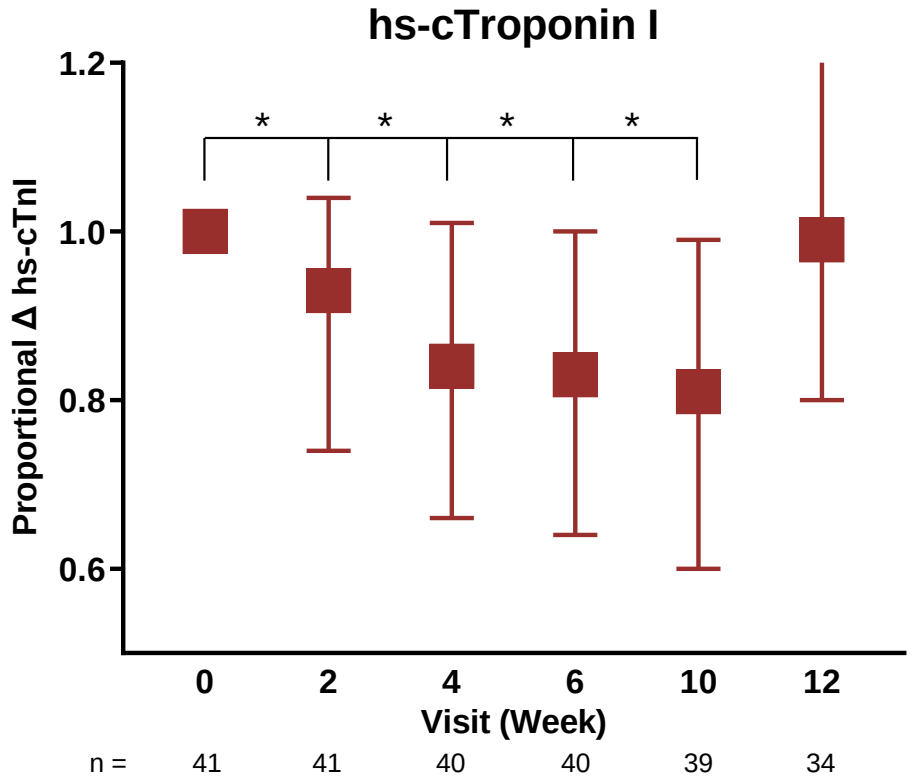

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Conclusions

- **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.

Long-Term Efficacy and Safety of *Aficamten* in Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy

Sara Saberi,[1] Theodore P. Abraham, Lubna Choudhury, Anjali T. Owens, Albree Tower-Rader, Florian Rader, Pablo Garcia-Pavia, Iacopo Olivotto, Caroline Coats, Michael A. Fifer, Scott D. Solomon, Hugh Watkins, Stephen B. Heitner, Daniel Jacoby, Stuart Kupfer, Fady I. Malik, Lisa Meng, Amy Wohltman, Martin S. Maron, Ahmad Masri, and the FOREST-HCM Investigators

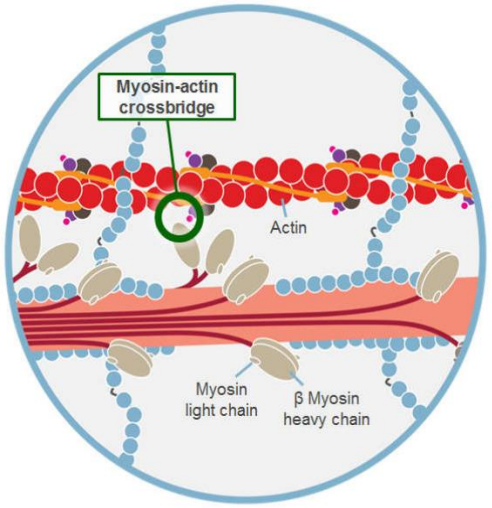
Cytokinetics

Disclosure

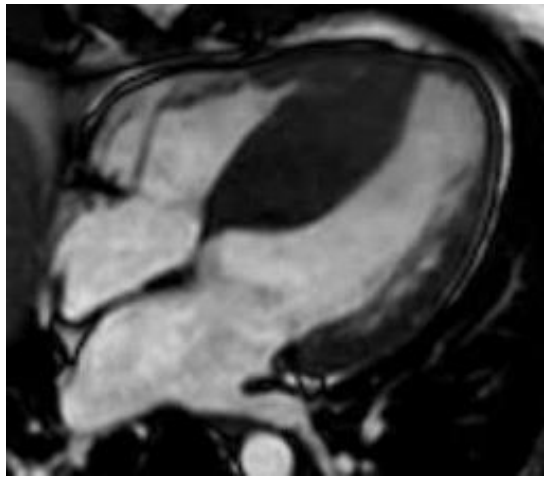
- **Dr Saberi** has received consultant/advisor fees from Bristol Myers Squibb and research grants from Bristol Myers Squibb, Cytokinetics, Novartis, and Actelion Pharmaceuticals

Background

- Hypertrophic cardiomyopathy (HCM)
  - Unexplained left ventricular hypertrophy
  - Hypercontractility
  - Abnormal relaxation
  - Myocardial fibrosis
  - Two-thirds have left ventricular outflow tract (LVOT) obstruction



- First-line therapies for obstructive HCM (oHCM) with beta-blockers, calcium channel blockers, and disopyramide do not address the underlying pathophysiology.



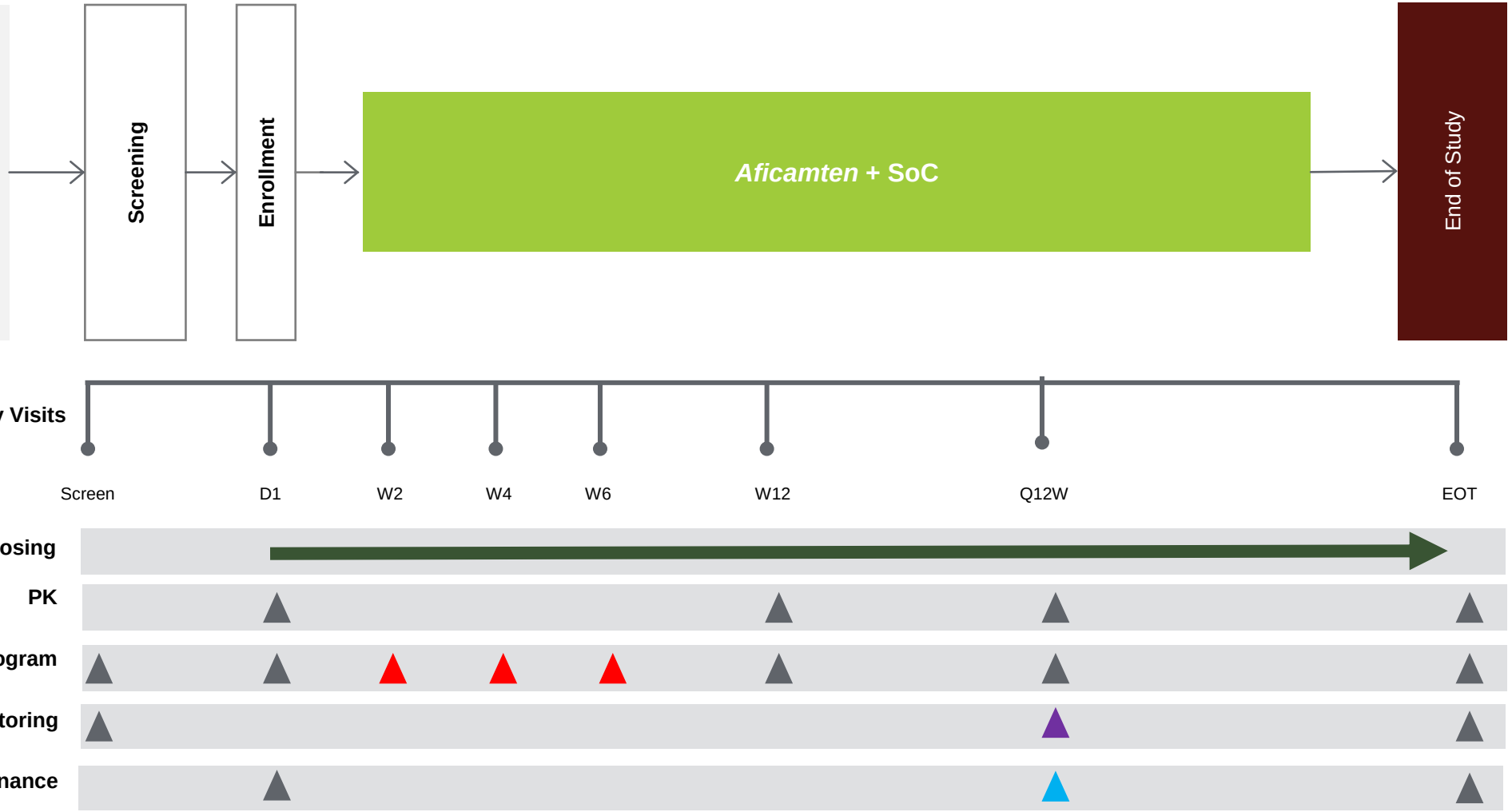
Background

- *Aficamten* is a next-in-class cardiac myosin inhibitor in development for the treatment of HCM
  - Reduces hypercontractility that underlies the pathophysiology of HCM[1]
  - Safe and effective in lowering resting and Valsalva LVOT gradients, improving heart failure symptoms, patient-reported outcomes (Kansas City Cardiomyopathy Questionnaire [KCCQ]), and biomarkers of wall stress and myocardial injury.
- FOREST-HCM (NCT04848506), formerly REDWOOD-HCM OLE, is an ongoing open-label extension study for eligible patients with oHCM or nonobstructive HCM (nHCM) who completed a parent study of *aficamten*.
- Here we report the interim safety and efficacy of *aficamten* in patients with oHCM in FOREST-HCM over 48 weeks.

Maron MS, et al. *J Am Coll Cardiol* 2023;81:34-45.

Study Schema

- Completion of a Cytokinetics trial investigating *aficamten*
- LVEF ≥55%



Truncated Echo

Occurs at Weeks 48, 96, 144, 192 and 240

Occurs at Weeks 48,144 and 240

Echo-guided dose titration that is managed by the investigator and can occur at any time during the trial

Methods

- Patients with oHCM were initiated on *aficamten* 5 mg and doses adjusted to 5–20 mg by site-read echo-based titration
  - Increase dose if LVEF ≥55% and Valsalva LVOT peak pressure gradient ≥30 mmHg
  - Decrease dose if LVEF <50%
  - Discontinue or interrupt if LVEF <40%

- Septal reduction therapy (SRT) eligibility criteria were presence of NYHA class III and peak LVOT gradient ≥50 mmHg

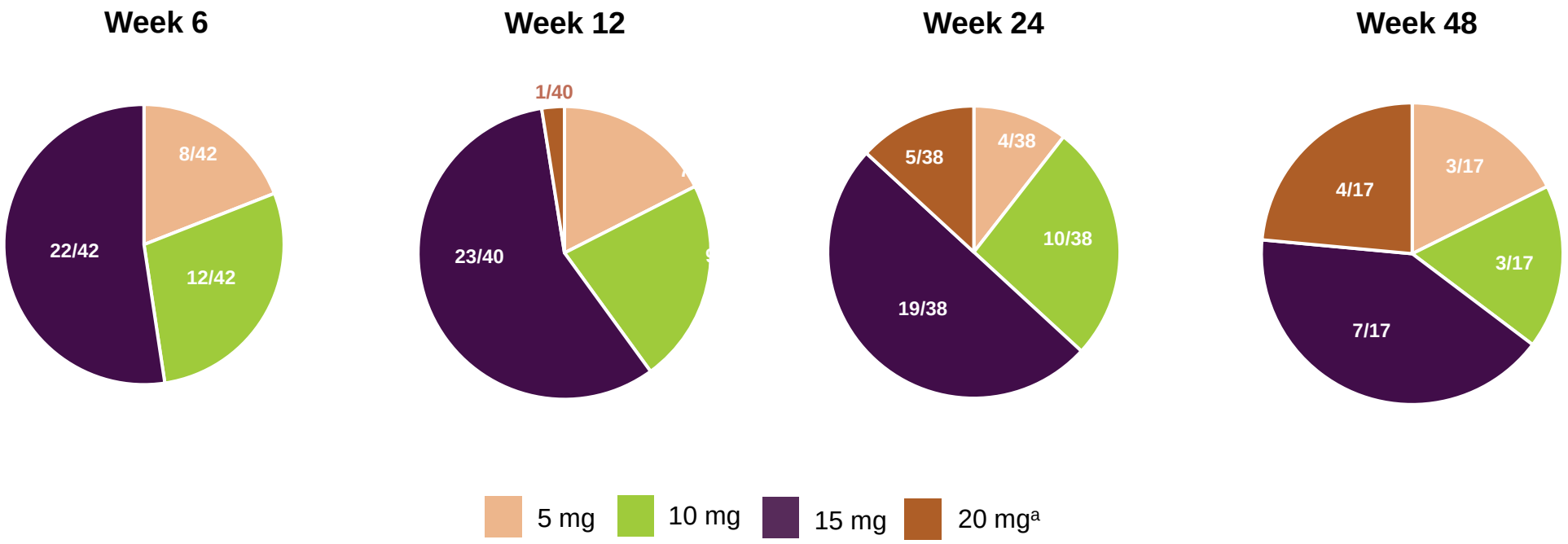
Results

- From May 2021 to September 2022, 45 patients with oHCM were enrolled.

Baseline Characteristics	Overall (N=45)
Age, mean ± SD (range), y	59.0 ± 12.8 (23–82)
Female, n (%)	26 (58)
Race, n (%)	
White	42 (93.3)
Black	2 (4.4)
Asian	1 (2.2)
BMI, mean ± SD (range), kg/m^2	29.9 ± 6.3 (22–51)
NYHA class, n (%)	
Class II	24 (53.3)
Class III	21 (46.7)

Baseline Characteristics, continued	Overall (N=45)
Positive family history of HCM, n (%)	10 (22.2)
Time since initial HCM diagnosis, mean ± SD (range), y	5.3 ± 5.4 (1–24)
Beta-blocker use, n (%)	35 (78)
Calcium channel blocker use, n (%)	8 (18)
Disopyramide use, n (%)	10 (22)
LVEF[a] at screening, mean ± SD, %	68.9 ± 4.7
LVOT-G[a], rest at screening, mean ± SD, mmHg	47 ± 26
LVOT-G[a], Valsalva at screening, mean ± SD, mmHg	80 ± 30
Eligible for septal reduction therapy, n (%)	19 (42)

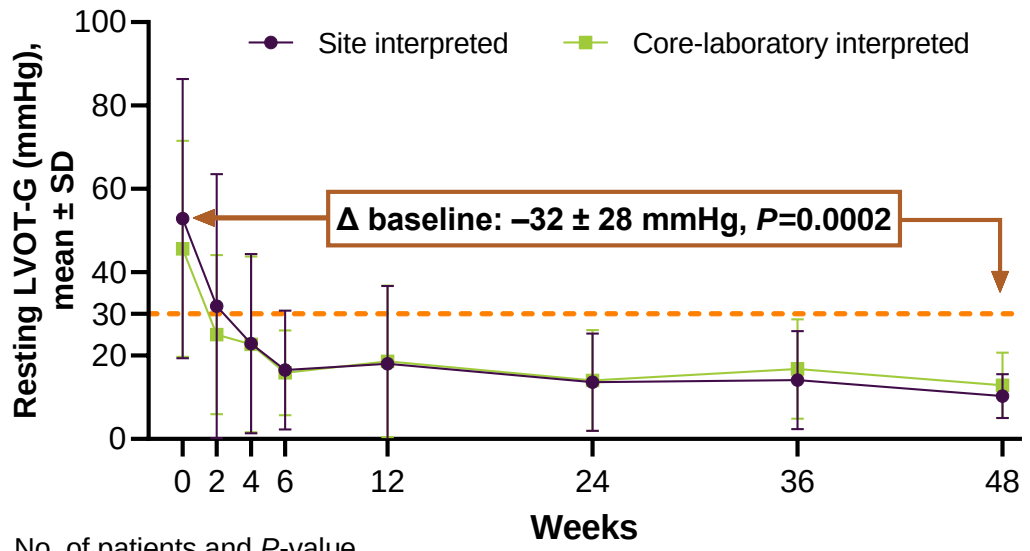
Figure 1: *Aficamten* Dose Achieved



[a] Titration to 20 mg was introduced with protocol amendment 3, which was finalized on Dec 15, 2021

Figure 2: (A) Resting LVOT-G and (B) Valsalva LVOT-G

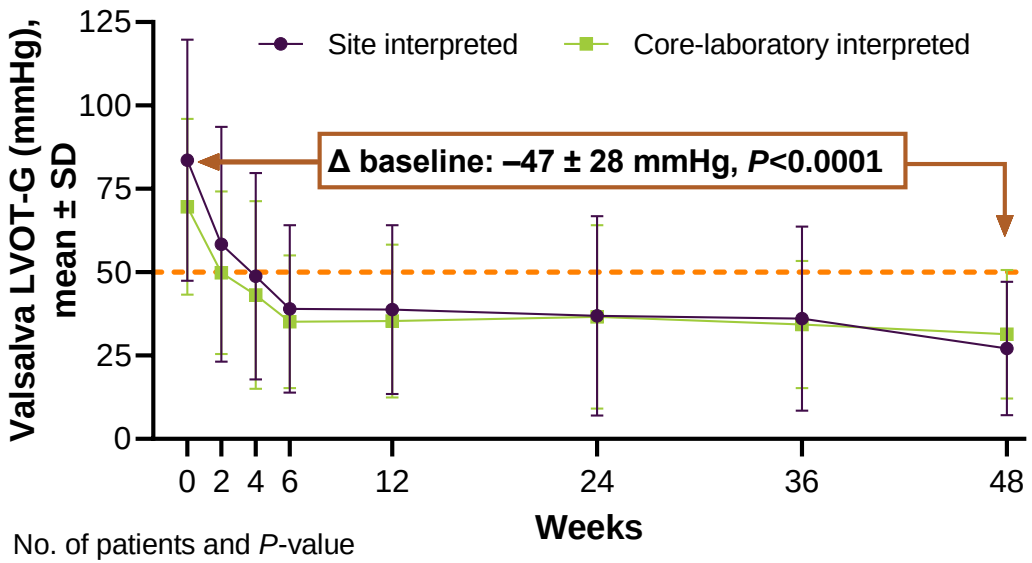
A



No. of patients and *P*-value

Core	35	35‡	35‡	35‡	32‡	38‡	26‡	15†
Site	45	45‡	43‡	43‡	40‡	38‡	27‡	17†

B



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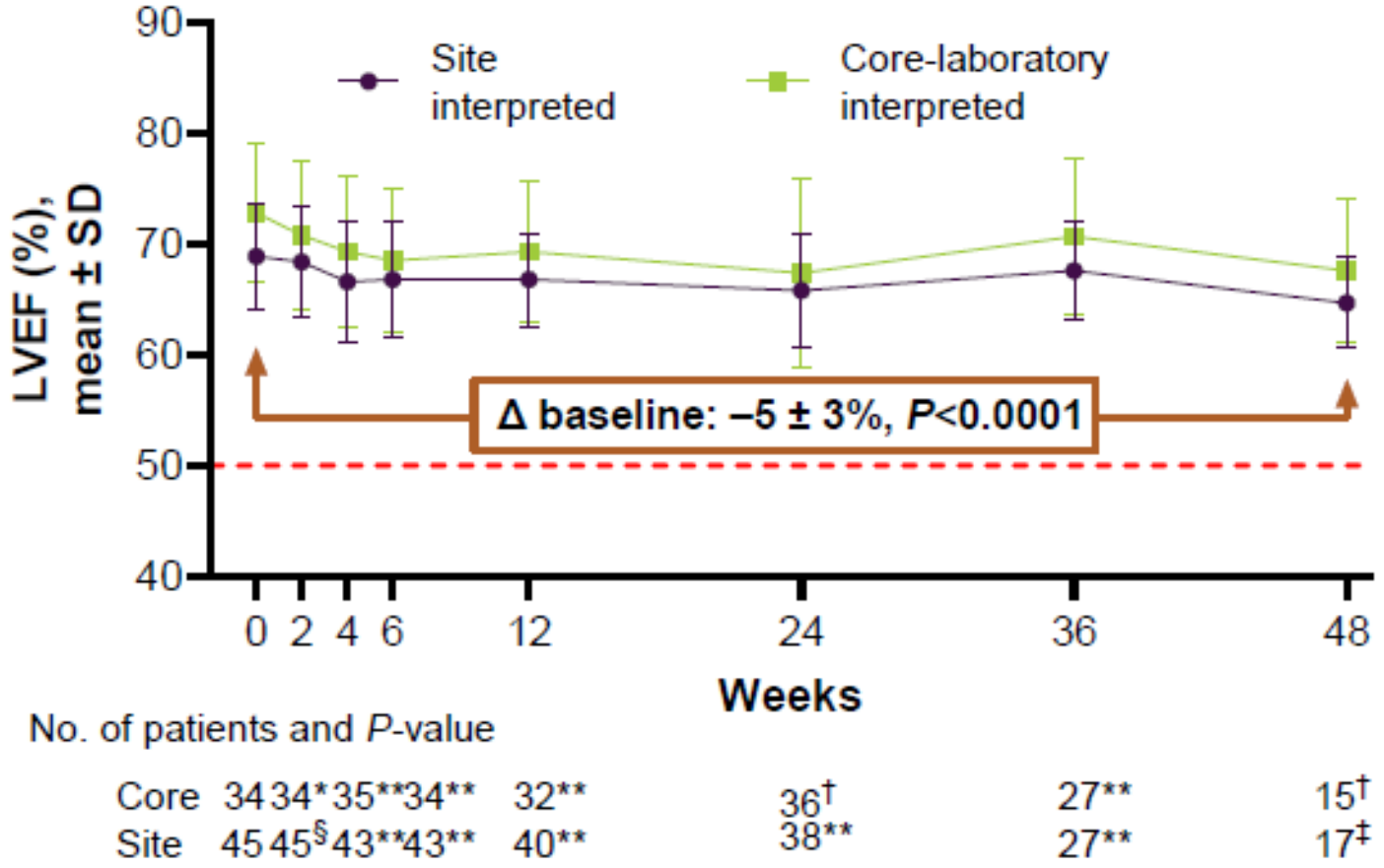
Core	35	35†	35‡	35‡	32‡	38‡	27‡	15†
Site	45	45‡	43‡	43‡	40‡	38‡	27‡	17‡

*P<0.05; **P<0.01; †P<0.001; ‡P<0.0001

Figure 3: LVEF



§P=0.45; *P<0.05; **P<0.01; †P<0.001; ‡P<0.0001.

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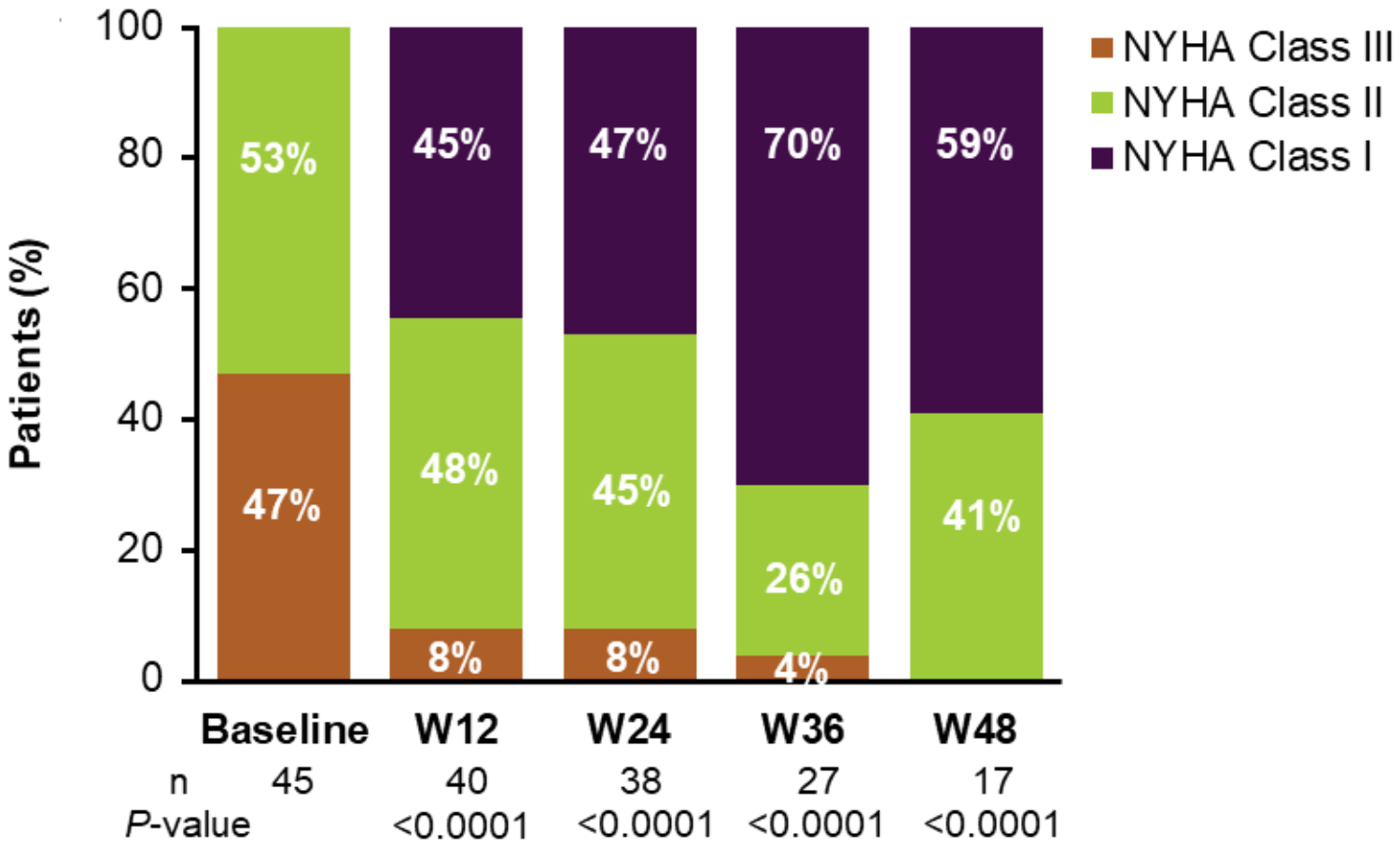

- By Week 48, 88% of patients experienced ≥1 NYHA FC improvement while none had NYHA FC worsening

P-value calculated as ≥1 class improvement vs baseline; using 1-sample test with the null hypothesis that proportion of NYHA improvement is 30%.

SRT Eligibility Criteria

- At baseline, 19 patients (42%) were eligible for SRT per guideline criteria of symptoms and hemodynamics, despite receiving beta-blocker (78%), calcium channel blocker (18%), and disopyramide (22%).

- Compared with baseline, by ≥ 6 months, none of the patients met these criteria.

NT-proBNP

- NT-proBNP decreased from baseline to Week 48 (from a geometric mean [CV%] of 651.0 [160.4] to 111.1 [93.4] pg/mL), representing a 70% reduction from baseline (P<0.0001).

Safety

- *Aficamten* was well tolerated with no treatment-related SAEs reported up to 48 weeks of treatment.

- One patient underwent temporary dose reduction (site error) and another had a temporary dose interruption (recurrent alcohol-induced atrial fibrillation).

Conclusions

- In this long-term study, treatment with *aficamten* in patients with oHCM was appropriately managed by investigators and was shown to be safe and well tolerated up to 48 weeks.
- Treatment with *aficamten* was associated with rapid and sustained improvements in echocardiographic hemodynamics paralleled by significant improvements in NYHA class.
- *Aficamten* eliminated SRT eligibility in patients who were guideline-eligible at baseline.
- There were no instances of systolic dysfunction (LVEF <50%) attributed to *aficamten*.
- These data support the continued development of *aficamten*, which is currently being investigated in the Phase III clinical trial SEQUOIA-HCM, and the planned head-to-head comparison of *aficamten* against metoprolol (CY 6032).