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Clinical Implications Associated With Temporary Treatment Interruption and Reinitiation of Aficamten Therapy in Obstructive Hypertrophic Cardiomyopathy

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- Investigators and study site staff
- Steering Committee members

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Background

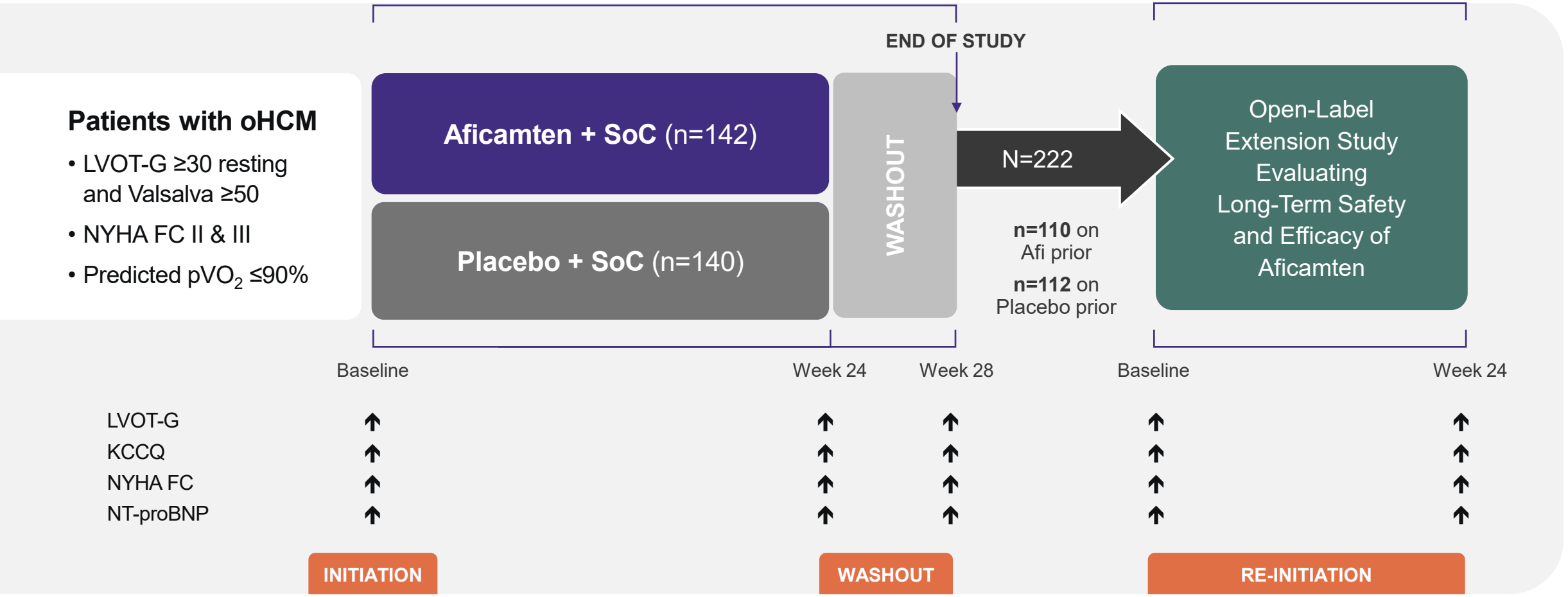
- Aficamten is a novel cardiac myosin inhibitor demonstrated in SEQUOIA-HCM to significantly lower outflow gradients and substantially improve symptoms, functional capacity and biomarkers
- Aficamten was recently approved for treatment of symptomatic obstructive HCM (oHCM)
- In clinical practice, patients with oHCM may require temporary cessation of medications, including aficamten (ie, surgery, illness)
- We evaluated outcomes associated with per-protocol temporary interruption of aficamten at completion of SEQUOIA-HCM and then after re-initiation in FOREST-HCM

Methods

- We characterized trajectory of LVOT-G, NYHA, KCCQ and NT-proBNP with aficamten following 4-week washout vs pre-treatment values and placebo in the 24-week SEQUOIA-HCM trial
- To further clarify return to baseline disease physiology (disease recurrence) vs deterioration beyond baseline (potential rebound), we identified patients with the following changes after washout (Week 28) vs baseline (Day 1):
  - >10% increase in resting or Valsalva gradients
  - ≥1 increase in NYHA class, and
  - ≥30% increase in NT-proBNP
- Treatment-emergent adverse events, including serious adverse events, were also assessed
- The same clinical outcome measures were evaluated after re-initiation of aficamten in FOREST-HCM to characterize consistency of response after treatment resumption

LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA FC, New York Heart Association functional class.

Study Schema



Afi, aficamten; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; oHCM, obstructive hypertrophic cardiomyopathy; pVO_2, peak oxygen uptake; SoC, standard of care.

Baseline Characteristics

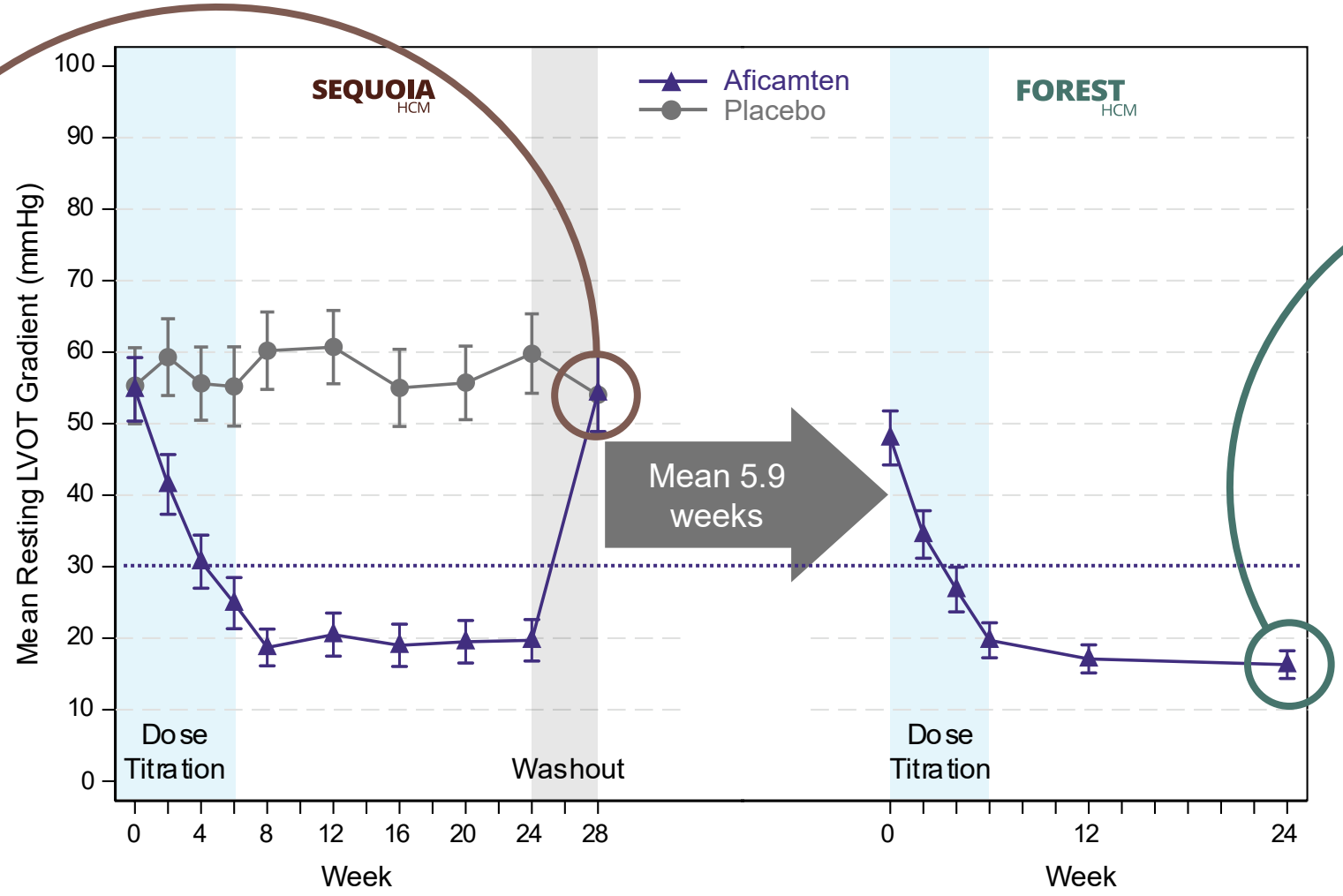
Characteristic	Aficamten (n=142)	Placebo (n=140)	Rollover (N=222)
Age, mean (SD), y	59 (12)	59 (13)	60.6 (13)
Male sex, n (%)	86 (61)	81 (58)	130 (59)
Race, n (%)			
White	108 (76)	115 (82)	210 (95)
Black	3 (2.1)	0	2 (0.9)
Asian	29 (20)	25 (18)	8 (4)
Body mass index, mean (SD), kg/m²	28(4)	28 (4)	28.6 (4)
NYHA class, n (%)			
II	108 (76)	106 (76)	157 (71)
III	34 (24)	33 (24)	64 (29)
IV	0	1 (0.7)	1 (0.5)
Post-Valsalva LVOT-G, mean (SD), mmHg	82.9 (32)	83.3 (33)	96.2 (38)
Resting LVOT-G, mean (SD), mmHg	54.8 (27)	55.3 (32)	57.2 (31)
NT-proBNP, mean (SD), pg/mL	1314 (1769)	1229 (1290)	1174 (1200)
KCCQ Clinical Summary Score, mean (SD)	75.6 (18)	73.7 (18)	72.6 (19)
Left ventricular ejection fraction, mean (SD), %	75 (5.5)	75 (6.3)	68.8 (7)

KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT-G, left ventricular outflow tract gradient; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association

Change in Rest LVOT-G after 4-week Washout of Aficamten vs Baseline and Placebo and Subsequent Re-initiation

After 4-Week Aficamten Washout:

LVOT-G Similar vs Baseline and vs Placebo (*P*=NS)



Re-initiation of Aficamten:

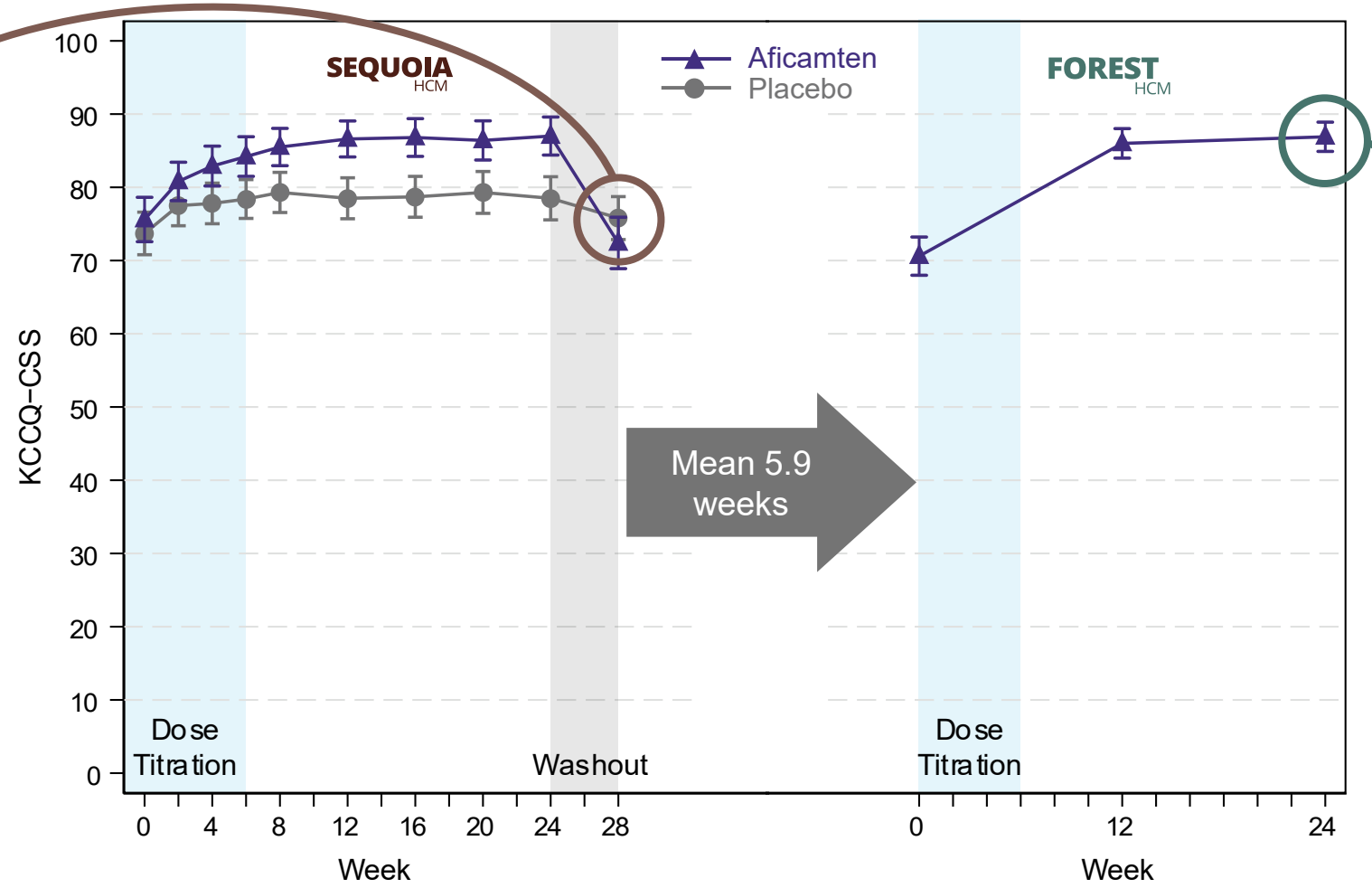
Change in LVOT-G at Week 24 Similar vs SEQUOIA-HCM Week 24 (*P*=NS)

LVOT-G, left ventricular outflow tract gradient; NS, non-significant.

Change in KCCQ-CSS after 4-week Washout of Aficamten vs Baseline and Placebo and Subsequent Re-initiation

After 4-Week Aficamten Washout:

KCCQ Lower vs Baseline and vs Placebo (*P*<0.01 for all)



Re-initiation of Aficamten:

Change in KCCQ at Week 24

Similar vs

SEQUOIA-HCM Week 24

(*P*=NS)

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NS, non-significant.

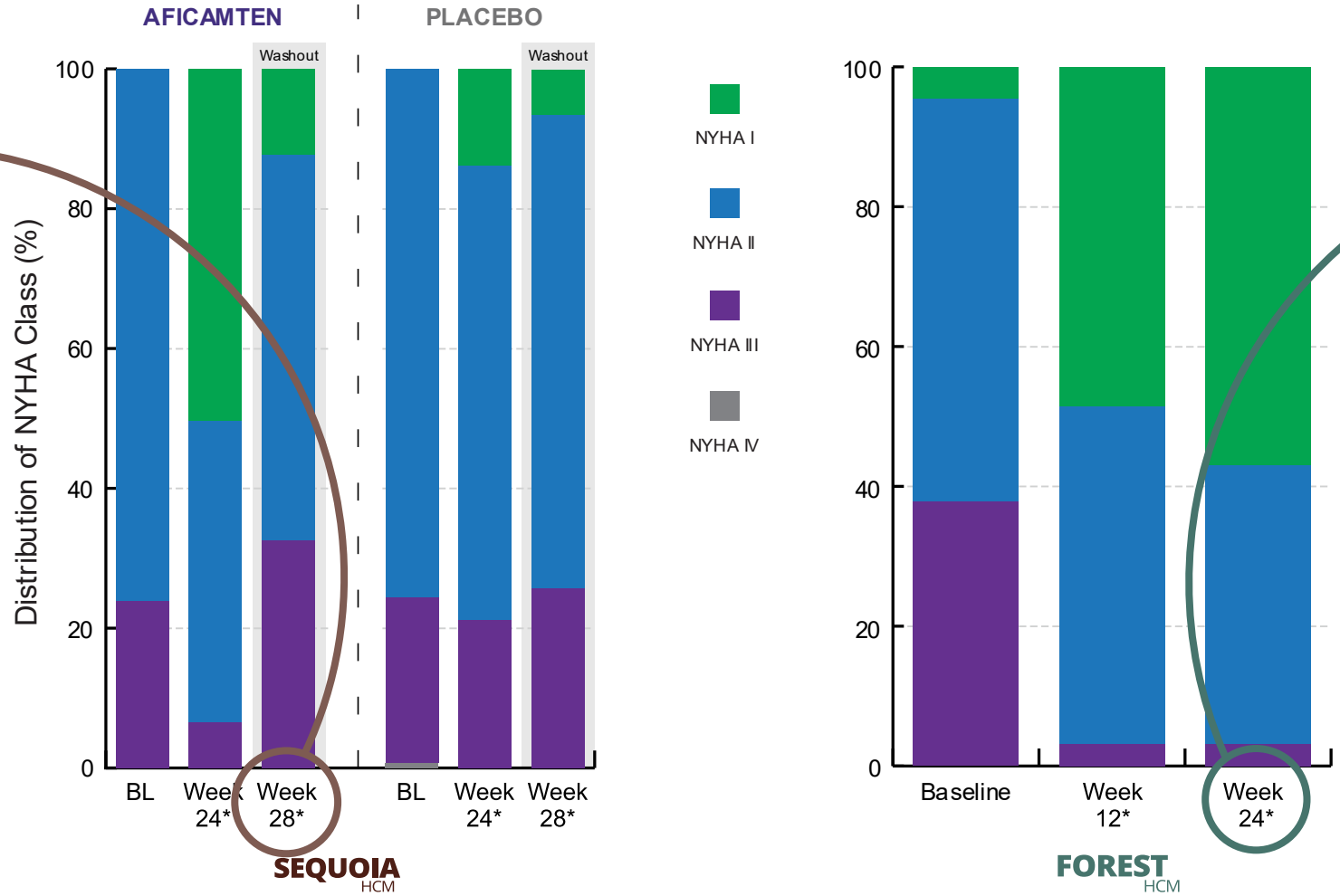
Change in NYHA Class after 4-week Washout of Aficamten vs Placebo and Subsequent Re-initiation

After 4-Week Aficamten Washout:

No difference in the proportion of NYHA classes vs Placebo

(*P*=NS)

SEQUOIA HCM



Re-initiation of Aficamten:

≥1 NYHA Class Improvement

Similar vs

SEQUOIA-HCM Week 24

(*P*=NS)

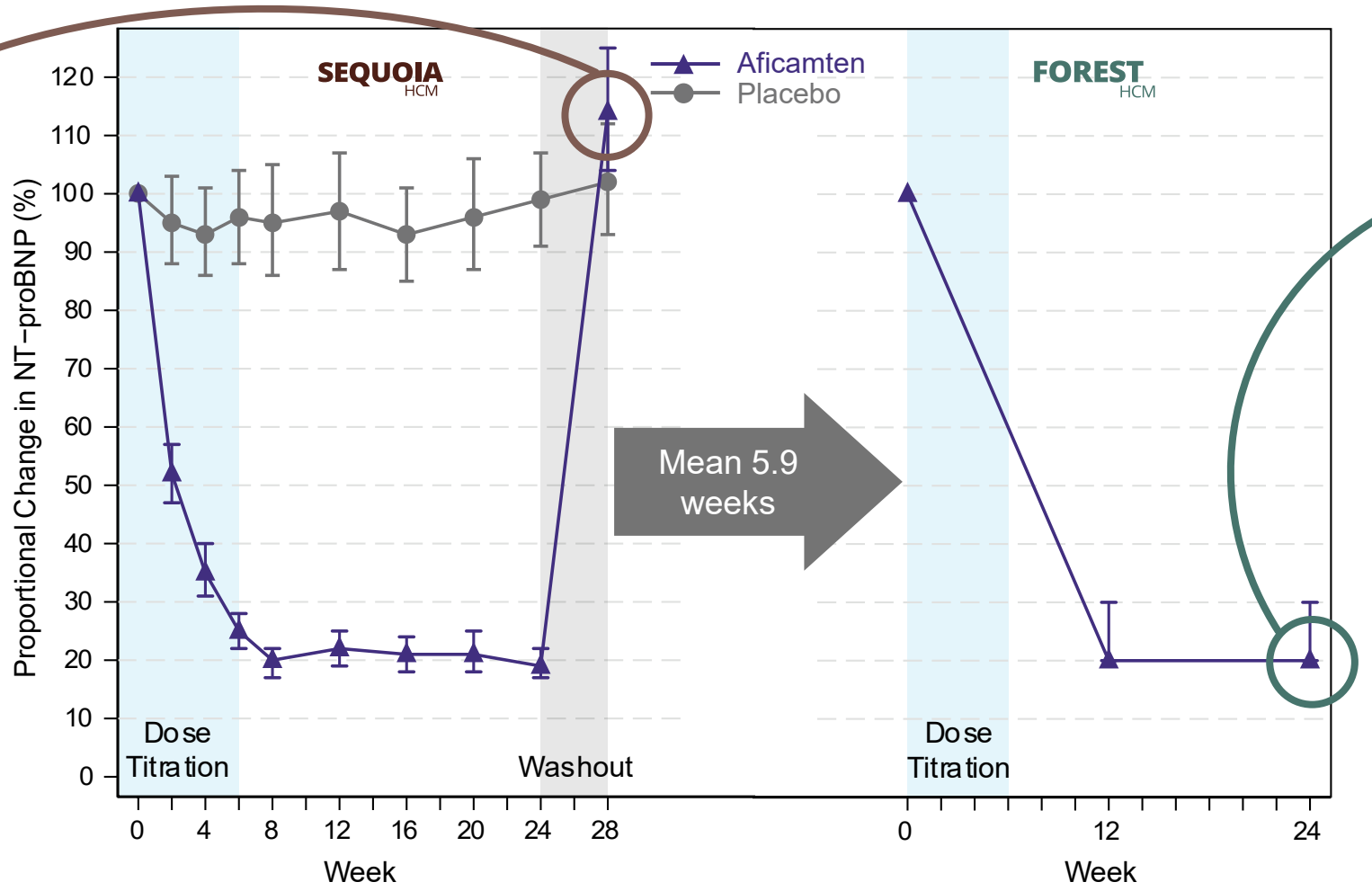
FOREST HCM

* Percentages were calculated based on patients with available data.
BL, Baseline; NYHA, New York Heart Association; NS, non-significant.

Change in NT-proBNP after 4-week Washout of Aficamten vs Baseline and Placebo and Subsequent Re-initiation

After 4-Week Aficamten Washout:

NT-proBNP higher vs Baseline (*P*=0.017) but similar vs Placebo (*P*=NS)



Re-initiation of Aficamten:

Change in NT-proBNP at 24 weeks

Similar vs

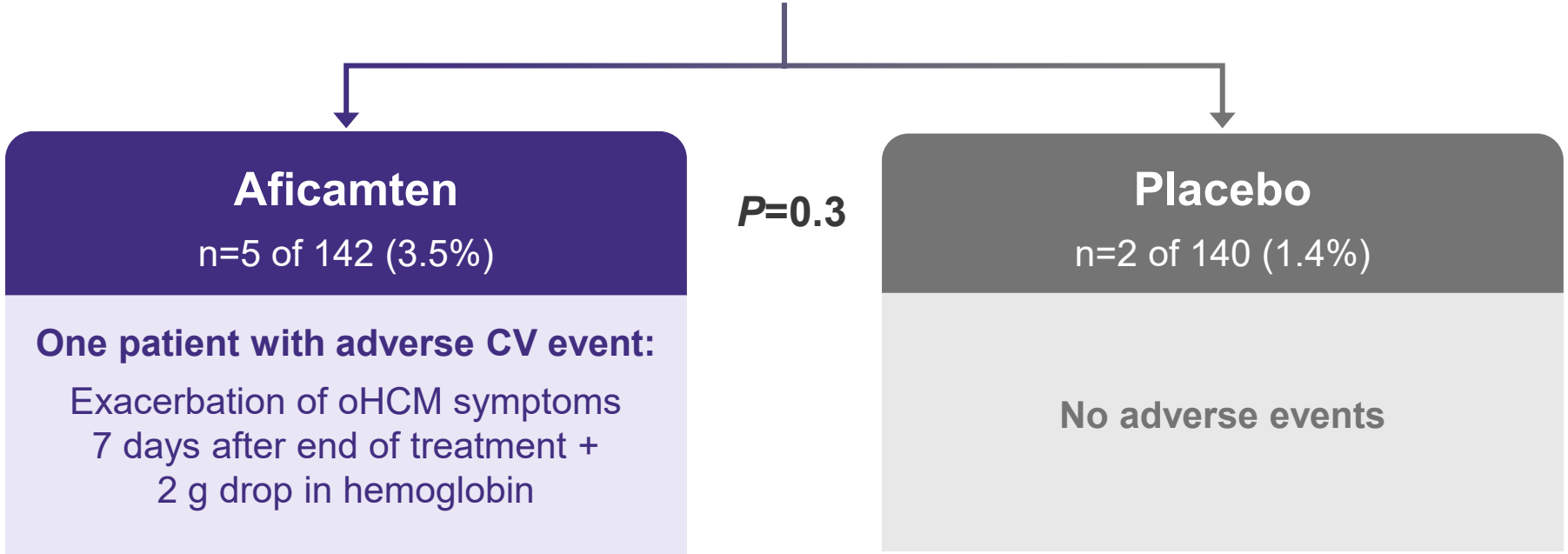
SEQUOIA-HCM Week 24

(*P*=NS)

NT-proBNP, N-terminal pro–B-type natriuretic peptide; NS, non-significant.

Potential Rebound

>10% increase in rest or Valsalva LVOT gradient,
≥1 increase in NYHA class and ≥30% increase in NT-proBNP



CV, cardiovascular; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy.

Serious Adverse Events During the Washout Occurred in 5 (3.5%) Treated with Aficamten vs 3 (2%) Placebo Patients:

Among Aficamten Patients During Washout Period:

- No Serious Adverse CV Events (Death, Cardiac Arrest, new AF, ICD Shock, or EF <50%)
- 4 Events were Noncardiac (Carotid Disease, Ischemic Stroke, Respiratory Failure, Anemia)
- 3 Events were Due to Recurrence of HCM Symptoms of Moderate Severity (Chest Pain and/or Dyspnea)
  - One ER Evaluation … Started Disopyramide (Resolved)
  - 2 inpatient admissions … Enrolled in FOREST-HCM (Resolved) and started Disopyramide (Resolved)

Conclusions

- Abrupt per-protocol cessation of aficamten in patients with oHCM was generally well tolerated and associated with a return to baseline physiology, including outflow tract obstruction, consistent with known reversal of drug effect

- Patients can experience recurrence of limiting symptoms (ie, SOB, CP, exertional fatigue), due to return of HCM pathophysiology, but no evidence of worse clinical deterioration (rebound effect) compared with pretreatment

- Re-initiation of aficamten provides similar favorable therapeutic response observed prior to cessation

- These findings suggest aficamten can be safely discontinued (acutely) if treatment interruptions are necessary (ie, surgery, illness)

CP, chest pain; oHCM, obstructive hypertrophic cardiomyopathy; SOB, shortness of breath