Safety and Outcomes of Standard of Care Medications Withdrawal in Patients with Obstructive Hypertrophic Cardiomyopathy Treated with Aficamten in FOREST-HCM Trial

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Speaker Disclosures

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Background

- Standard of care (SoC) medications for the treatment of obstructive hypertrophic cardiomyopathy (oHCM) are currently recommended as first-line therapy
  - None directly target the sarcomere
  - Side effects often render them poorly tolerated
- Completed aficamten trials recruited patients who remained symptomatic and obstructive on SoC therapy

Disopyramide
Urinary retention
Sedation, dizziness, confusion, hallucinations
Blurred vision, dry eyes
Tachycardia
Feeling hot, decreased sweating
Dry throat, dry mouth, constipation

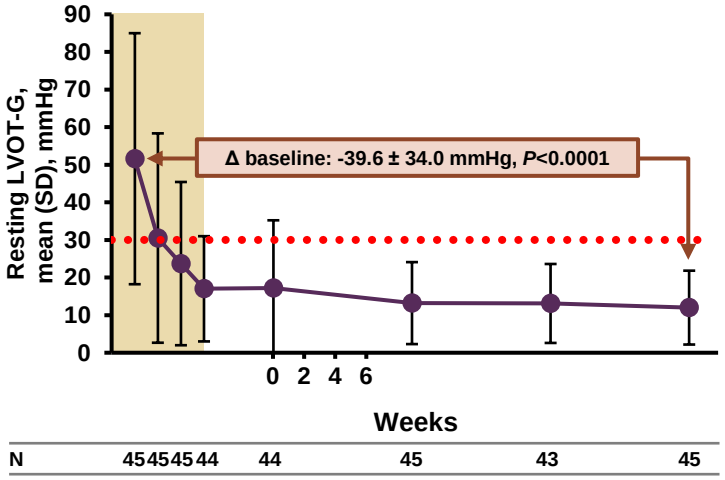
Calcium Channel Blockers (CCB)
Hypotension
Bradycardia
Dizziness
Peripheral edema
Constipation

Beta Blockers (BB)
Hypotension
Bradycardia
Fatigue
Insomnia
Sexual dysfunction

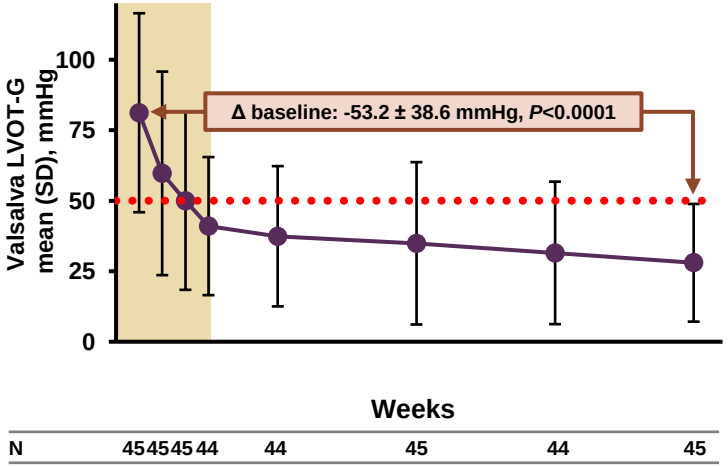
Aficamten is the Next-in-Class Cardiac Myosin Inhibitor

FOREST-HCM 48-weeks efficacy data

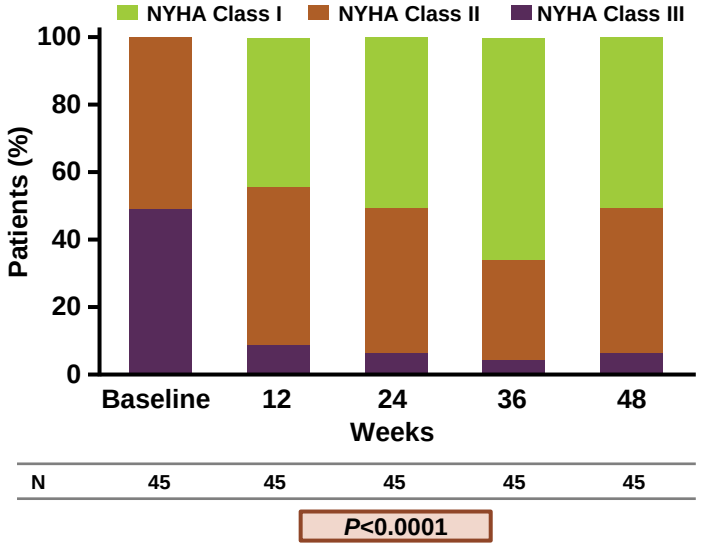
Resting LVOT-G



Valsalva LVOT-G



NYHA Class



By Week 48, 82.2% of patients experienced ≥1 NYHA class improvement (*P*<0.0001), none had NYHA class worsening

HCM, hypertrophic cardiomyopathy; LVOT-G, left ventricular outflow tract gradient; NYHA, New York Heart Association.

Methods and Aim

Aim:

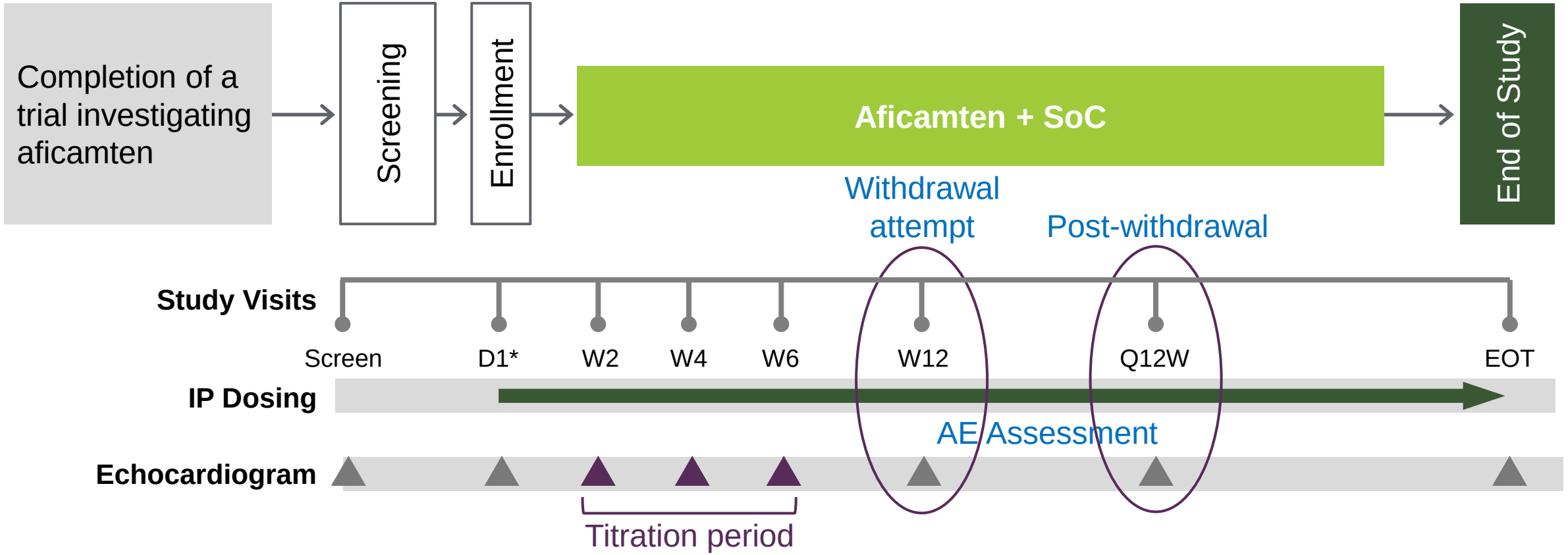
- To describe the impact of SoC therapy withdrawal in patients already being treated with aficamten in FOREST-HCM (NCT04848506)

Methods:

- Per protocol, PIs, at their discretion or at the request of the patient, were allowed to reduce or discontinue SoC therapy after patients had been on a stable dose of aficamten ≥4 weeks
  - The approach to down-titration of SoC therapy and discontinuation was at the discretion of the PI
  - Successful SoC therapy withdrawal was defined as dose-reduction of ≥1 SoC medication by at least ≥50% from baseline
  - Aficamten dose could be escalated if the follow-up echocardiography met the appropriate per-protocol criteria
- Patients had prespecified, per-protocol, safety follow-up (by phone or in person) 1-2 weeks after withdrawal or reduction of any SoC therapies
- A cohort of patients receiving aficamten who did not undergo SoC withdrawal was used as a comparator

PI, principal investigator.

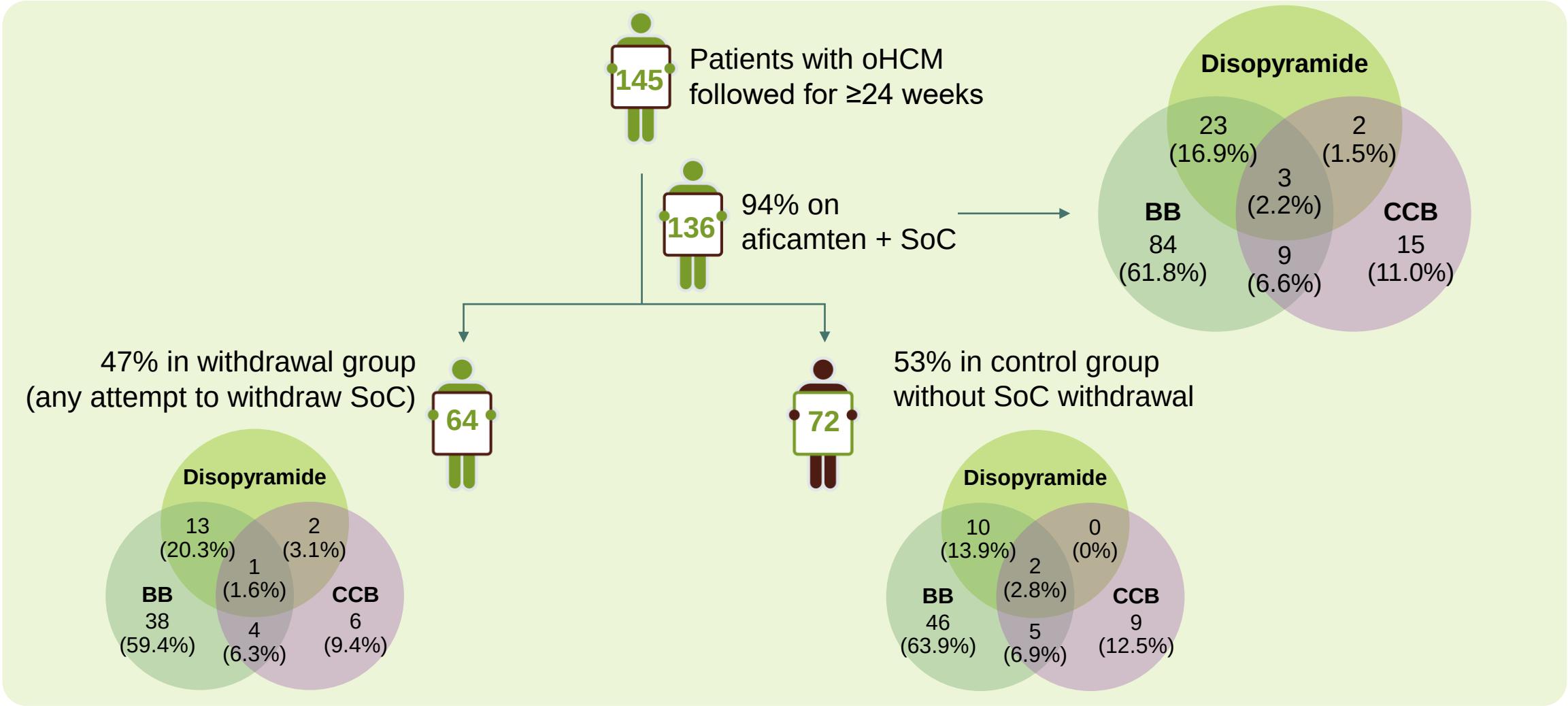
Methods



- SoC: BB's, CCB's, and Disopyramide allowed in any combination

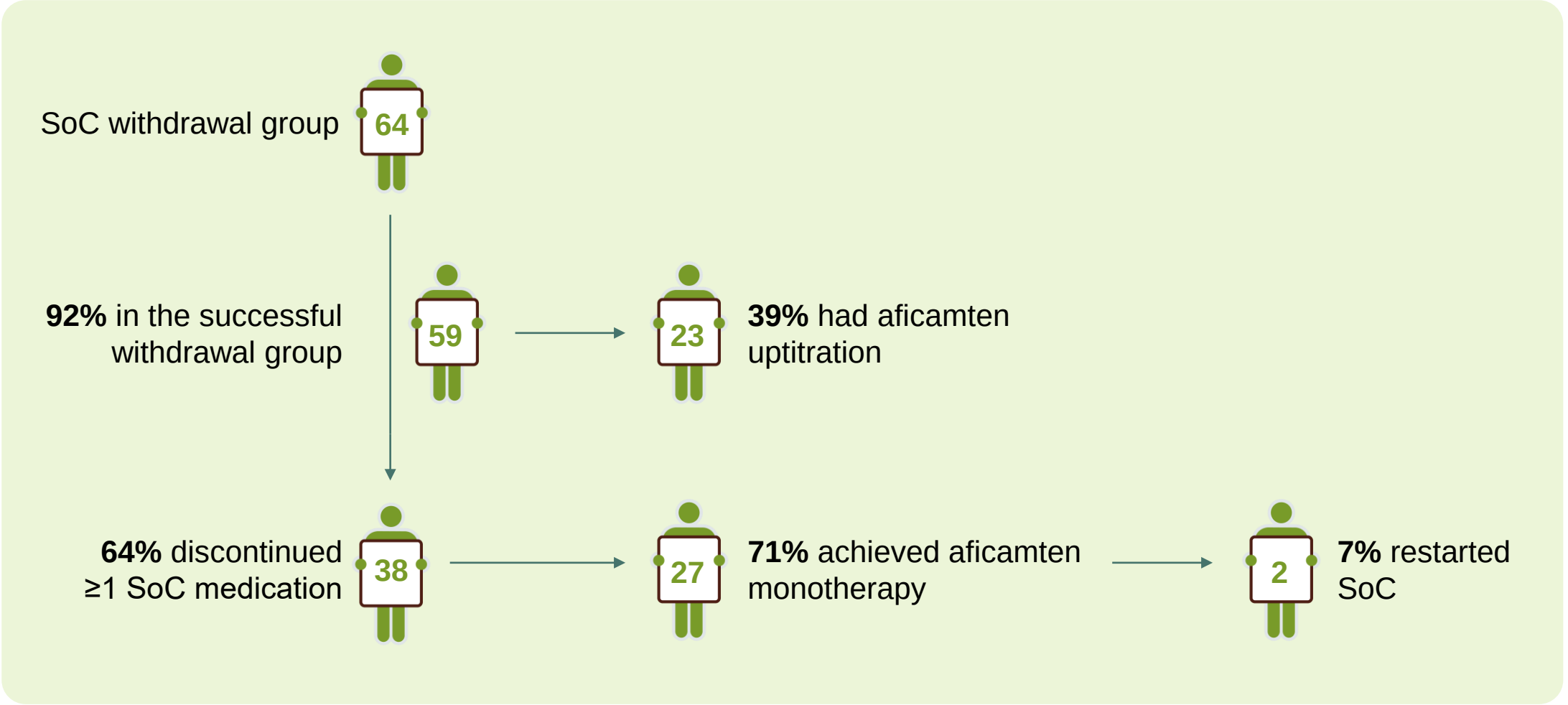
*Baseline Characteristics.
AE, adverse event; EOT, end of treatment; IP, investigational product.

Patient Disposition*



*Data cut-off February 15th, 2024.

Patient Disposition*



Baseline Characteristics

Variable	All Patients on SoC (N=136)	Patients with SoC Withdrawal Attempt (N=64)	Patients without SoC Withdrawal Attempt (N=72)
Age (Years), Mean (SD) [Range]	60.5 (13.2) [23, 84]	60.5 (13.8) [23, 84]	60.4 (12.7) [27, 83]
Female, n (%)	63 (46.3)	31 (48.4)	32 (44.4)
Race, % White/AA/Asian/Other	96/2/2	96/2/2	96/3/1
AF or flutter, n (%)	26 (19.1)	12 (18.8)	14 (19.4)
Hypertension, n (%)	57 (41.9)	24 (37.5)	33 (45.8)
Known HCM-causing gene mutation or positive family history, n (%)	46 (33.8)	18 (28.1)	28 (38.9)
NYHA Class, n (%)			
I	1 (0.7)	0	1 (1.4)
II	78 (57.4)	32 (50.0)	46 (63.9)
III	57 (41.9)	32 (50.0)	25 (34.7)
KCCQ-CSS Mean (SD) [Range]	71.0 (19.1) [10.4, 100]	68.7 (19.7) [10.4, 97.9]	73.0 (18.6) [32.3, 100]
Beta Blocker, n (%)	119 (87.5)	56 (87.5)	63 (87.5)
Calcium Channel Blocker, n (%)	29 (21.3)	13 (20.3)	16 (22.2)
Disopyramide, n (%)	28 (20.6)	16 (25.0)	12 (16.7)
Two or more SoC medications, n (%)	37 (27.2)	20 (31.3)	17 (23.6)

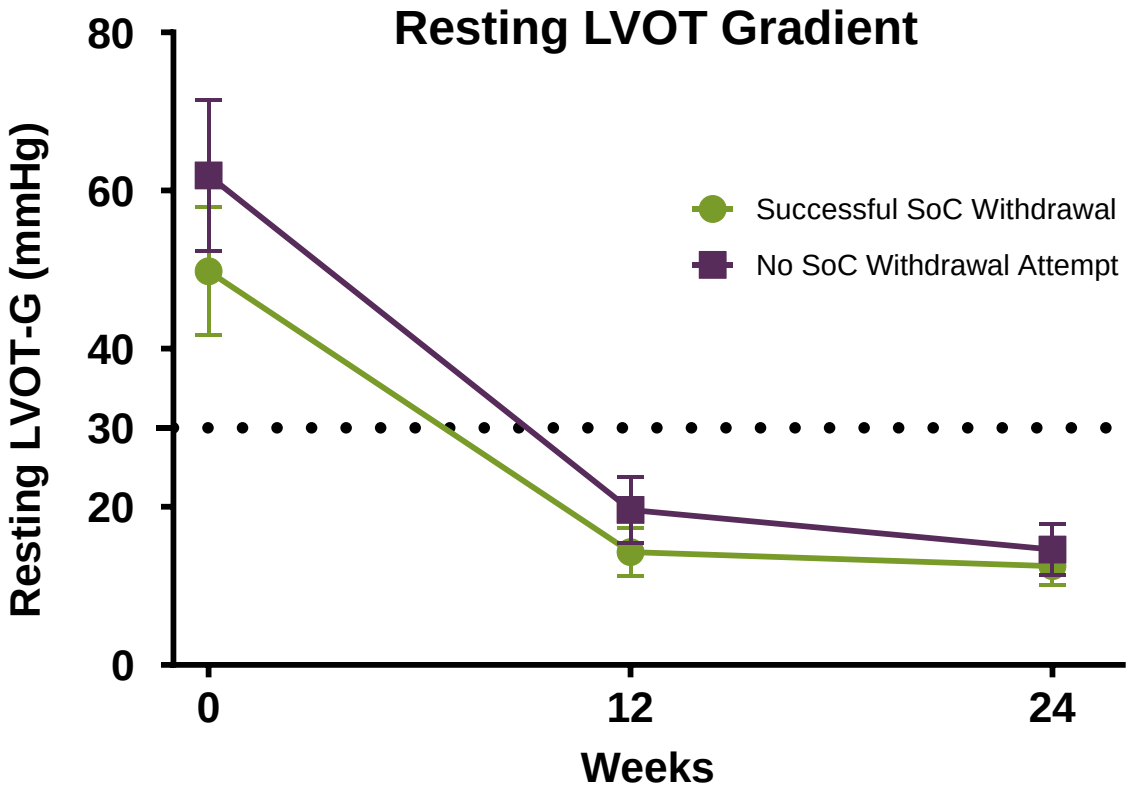
AF, atrial fibrillation; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; SD, standard deviation.

Baseline Characteristics

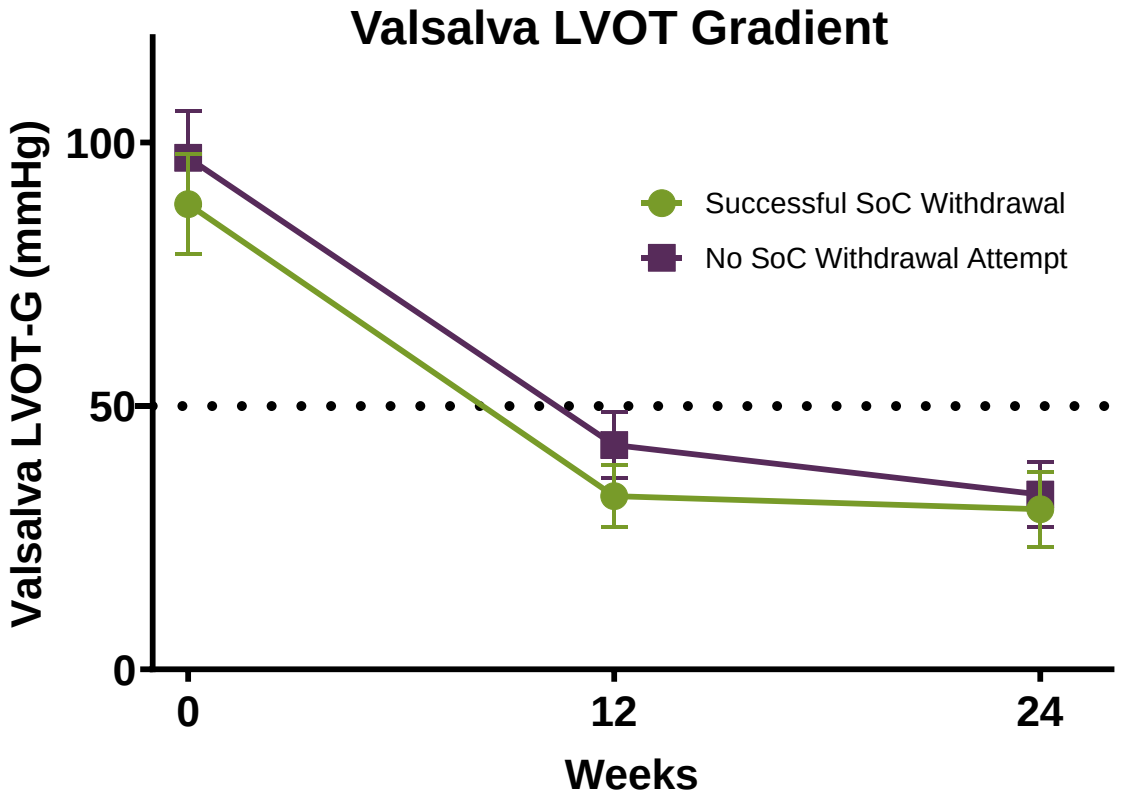
Variable	All Patients on SoC (N=136)	Patients with SoC Withdrawal Attempt (N=64)	Patients without SoC Withdrawal Attempt (N=72)
NT-proBNP (pg/mL) Median [Q1, Q3]	933.5 [387, 1874]	966 [387, 1643]	918.5 [382, 1946.5]
hs-cardiac-TnI (ng/L) Median [Q1, Q3]	12.2 [6.2, 19.8]	11.0 [5.4, 18.0]	12.5 [7.2, 23.0]
LVEF* (%), Mean (SD)	67.9 (5.7)	68.3 (5.8)	67.6 (5.7)
LVOT-G* rest (mmHg), Mean (SD)	57.8 (37.8)	53.0 (34.0)	61.9 (40.5)
LVOT-G* Valsalva (mmHg), Mean (SD)	95.6 (39.3)	94.0 (40.9)	97.1 (38.2)

*Site reported.
hs-cardiac-TnI, high-sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction; NT-proBNP; N-terminal pro b-type natriuretic peptide.

Efficacy of Aficamten was Maintained Independent of SoC Withdrawal



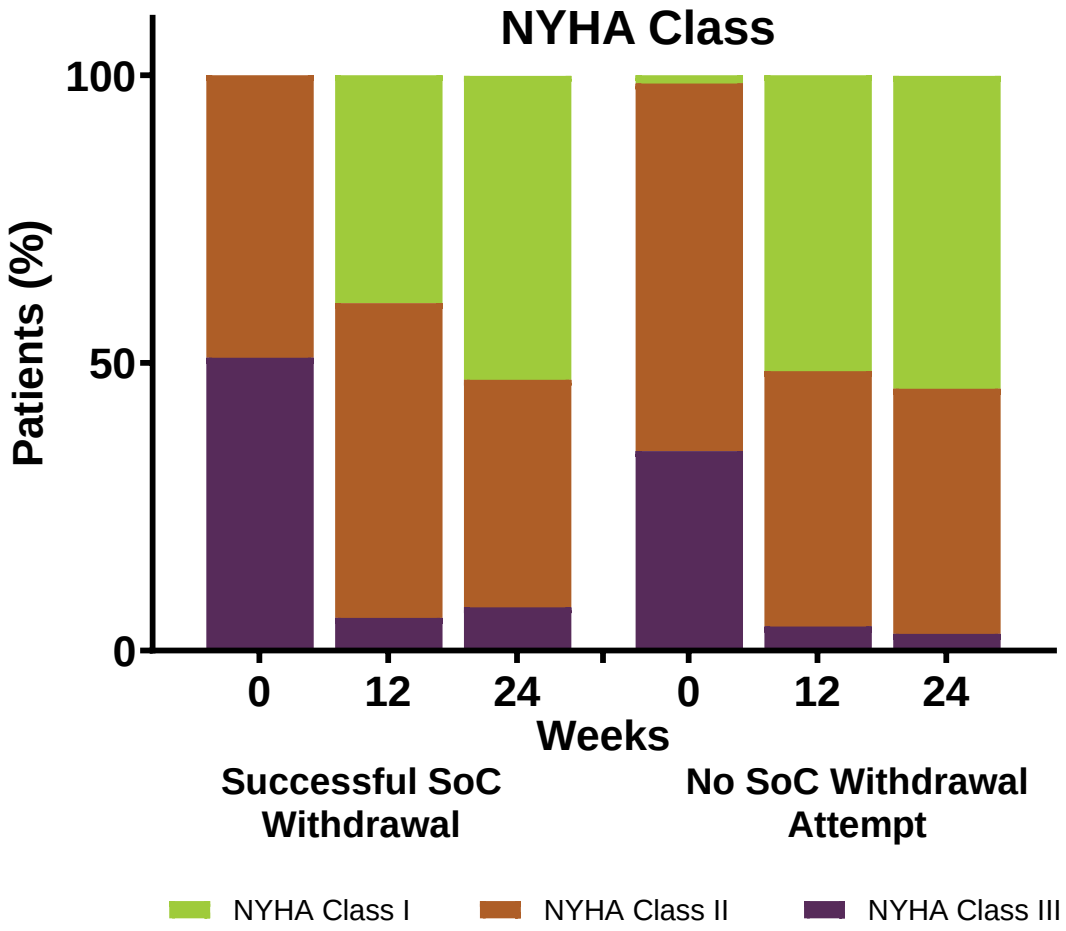
P-value Successful Withdrawal vs. No Withdrawal Attempt = NS
P-value Week 12 – Baseline <0.0001, Post-withdrawal – week 12= NS



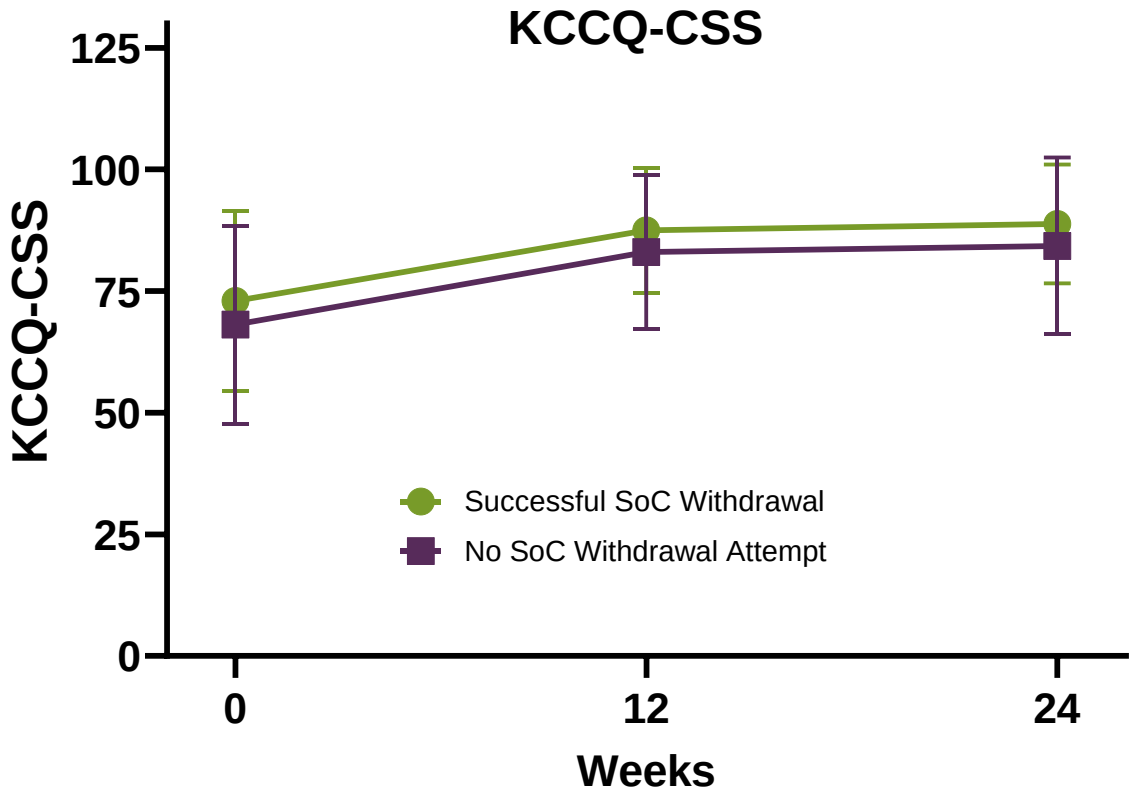
P-value Successful Withdrawal vs. No Withdrawal Attempt = NS
P-value Week 12 – Baseline <0.0001, Post-withdrawal – week 12= NS

Excluding 1 patient who had SoC withdrawal attempt at week 85.
NS, not significant.

Efficacy of Aficamten was Maintained Independent of SoC Withdrawal



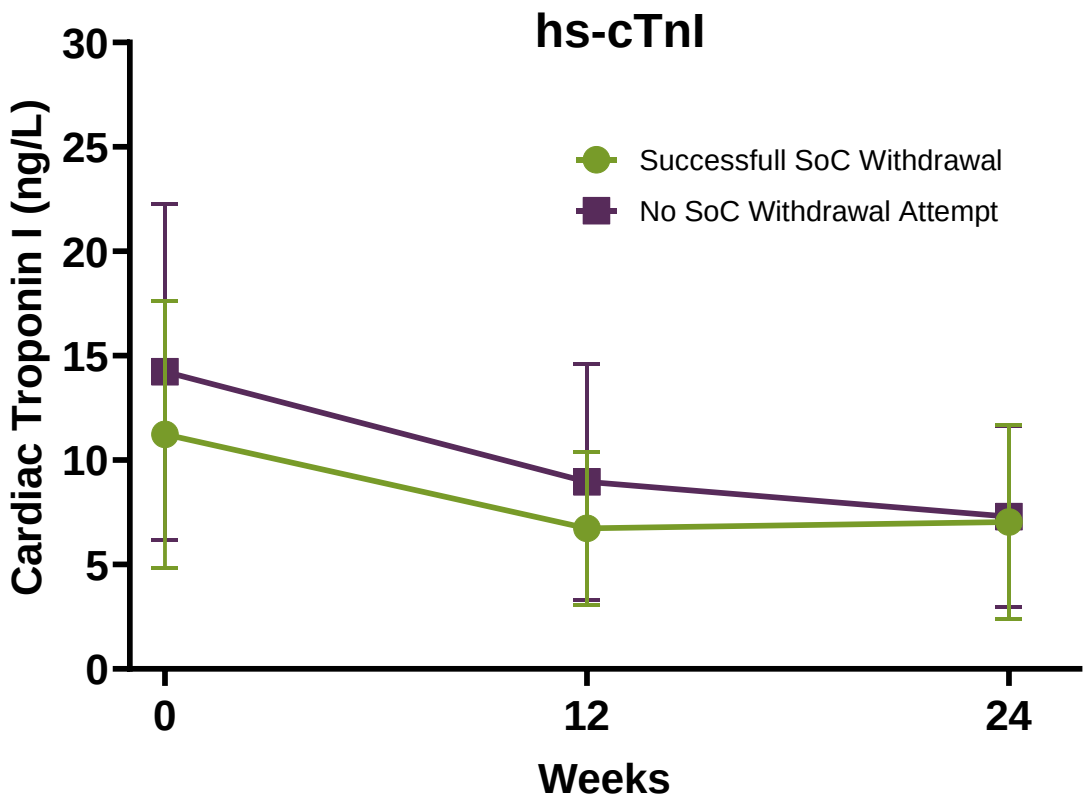
P-value With vs. Without Withdrawal Attempt = NS
P-value* Week 12 – Baseline <0.0001 With Successful Withdrawal; <0.0005 Without Withdrawal Attempt
P-value Post-withdrawal – Week 12 = NS



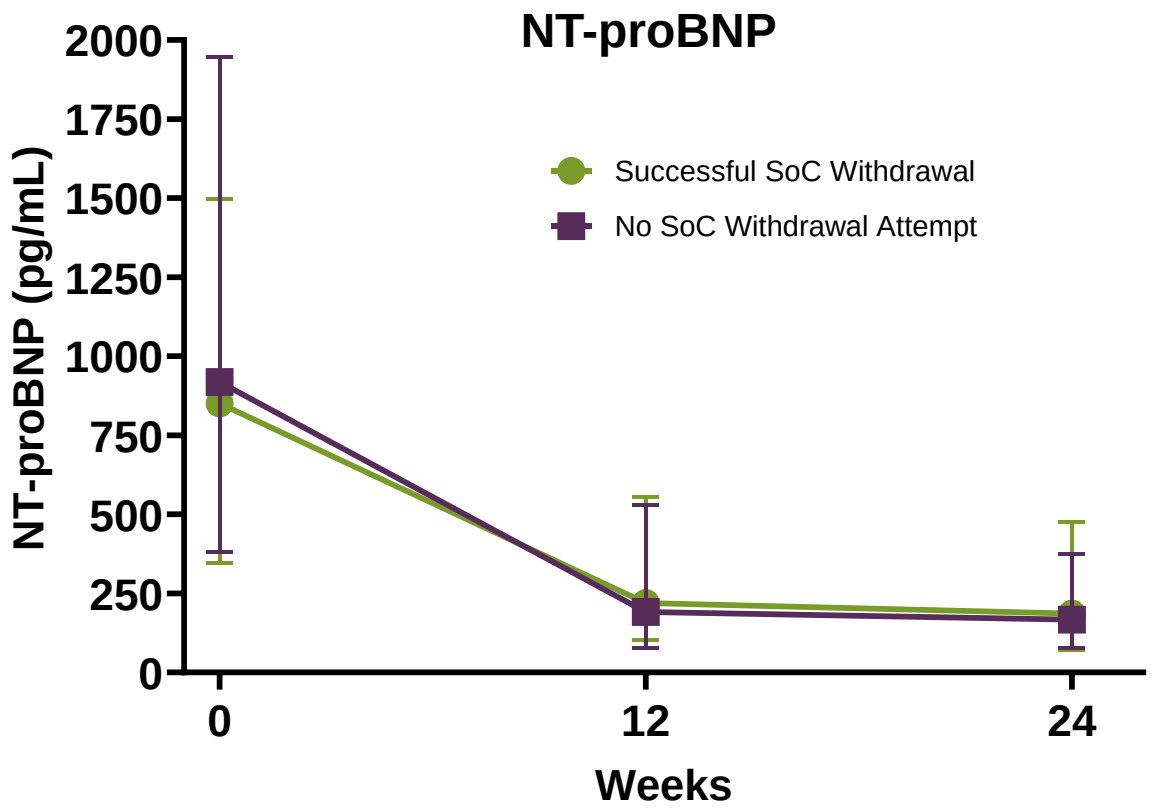
P-value With vs. Without Withdrawal Attempt = NS
P-value Week 12 – Baseline <0.0001, Post-withdrawal – Week 12 = NS

*Proportion of patients with ≥1 class improvement in NYHA class.
NS, not significant.

Change in Cardiac Biomarkers



P-value Successful SoC Withdrawal vs. No Withdrawal Attempt = NS
P-value Post-withdrawal– Week 12= NS



P-value Successful SoC Withdrawal vs. No Withdrawal Attempt= NS
P-value Post-withdrawal– Week 12= NS

Median, IQR.
NS, not significant.

Efficacy of Aficamten was Maintained Independent of SoC Withdrawal

	Successful SoC Withdrawal Group (N=59)				No Soc Withdrawal Group (N=72)				Between Group
	Baseline	Pre / Week 12	Post	*P*-value	Baseline	Week 12	Week 24	*P*-value	*P*-value
Symptoms									
NYHA Class, ≥ 1 Improvement (%)		79.2	83.0	0.75		75.0	76.5	1.0	0.70
KCCQ-CSS, Mean (SD)	68.1 (20.4)	83.0 (15.8)	84.3 (18.2)	0.43	73.0 (18.55)	87.5 (12.9)	88.8 (12.3)	0.23	0.98
Hemodynamics									
Heart rate (bpm)	64.5 (11.0)	66.0 (12.8)	70.7 (11.0)	0.002	61.4 (8.0)	64.7 (9.1)	62.1 (8.5)	0.005	<0.001
Systolic BP (mmHg)	123.7 (14.4)	129.0 (12.8)	128.3 (13.7)	0.66	123.1 (16.8)	128.4 (15.1)	131.8 (16.5)	0.04	0.09
Diastolic BP (mmHg)	71.5 (10.4)	75.4 (10.5)	75.5 (9.5)	0.91	71.5 (12.3)	76.3 (12.0)	78.1 (12.1)	0.05	0.24
LVEF* (%), Mean (SD)	69.0 (5.4)	65.9 (6.1)	65.0 (6.2)	0.22	67.6 (5.7)	65.3 (4.8)	64.6 (5.3)	0.28	0.77
LVOT-G*, Rest (mmHg), Mean (SD)	49.8 (29.2)	14.3 (10.9)	12.5 (9.2)	0.32	61.9 (40.5)	19.6 (18.0)	14.6 (13.7)	0.003	0.19
LVOT-G*, Valsalva (mmHg), Mean (SD)	88.3 (34.2)	32.9 (21.4)	30.4 (25.5)	0.55	97.1 (38.2)	42.6 (26.3)	33.2 (25.6)	0.002	0.17
Biomarkers									
NT-proBNP (pg/mL) median [Q1, Q3]	851 [346, 1498]	220 [102.0, 554]	186 [72.0, 475]	0.81	918.5 [382, 1946.5]	191.5 [78.0, 531.0]	167.5 [76.0, 376.0]	0.75	0.96
hs-cardiac-TnI (ng/L), Median [Q1, Q3]	10.7 [5.1, 17.9]	6.0 [3.5, 10.7]	5.3 [3.5, 12.3]	1.00	12.5 [7.2, 23.0]	7.6 [4.1, 15.2]	6.2 [3.6, 12.1]	0.35	0.37

*Site read echo results.
BP, blood pressure.

Safety of Aficamten was Maintained in the SoC Withdrawal Group

N (%)	Patients with Standard of Care Withdrawal Attempt (N=64)	Patients without Standard of Care Withdrawal Attempt (N=72)
Patients with at least one TEAE	47 (73.4)	50 (69.4)
Patients with TESAEs	12 (18.8)	6 (8.3)
Patients with fatal TEAEs	0	0
Patients with TEAEs leading to drug interruption	3 (4.7)	1(1.4)
Patients with TEAEs leading to dose reduction	2 (3.1)	3 (4.2)
Patients with AEs related to study drug (per investigator)	5 (7.8)	13 (18.1)
LVEF < 50%	3 (4.7)	2 (2.8)
Atrial fibrillation or flutter	5 (7.8)	3 (4.2)
New Onset	1 (1.6)	0
Recurrent	4 (6.3)	3 (4.2)

TEAE, treatment-emergent adverse event.

Conclusions

- Patients with oHCM in FOREST-HCM frequently underwent successful withdrawal of SoC medications while on aficamten treatment without negatively impacting hemodynamics, symptoms, or cardiac biomarkers, when compared to pre-withdrawal values.

- The treatment effect of aficamten was not meaningfully different in patients who underwent SOC withdrawal compared to patients who did not undergo SOC withdrawal.

- SoC withdrawal did not impact the safety of aficamten.

- These data support the further study of aficamten as monotherapy in oHCM and provides guidance on the expected outcomes of withdrawal of SoC therapies in oHCM.

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Acknowledgements

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