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Standard-of-Care Medication Withdrawal in Patients With Obstructive Hypertrophic Cardiomyopathy Receiving Aficamten in FOREST-HCM

Ahmad Masri, MD, MS,[a] Lubna Choudhury, MD, MRCPI,[b] Roberto Barriales-Villa, MD,[c] Perry Elliott, MBBS, MD,[d] Martin S. Maron, MD,[e] Michael E. Nassif, MD,[f] Artur Oreziak, MD, PhD,[g] Anjali Tiku Owens, MD,[h] Sara Saberi, MD,[i] Albree Tower-Rader, MD,[j] Florian Rader, MD, MSc,[k] Pablo Garcia-Pavia, MD, PhD,[l,m] Iacopo Olivotto, MD,[n] Sherif F. Nagueh, MD,[o] Andrew Wang, MD,[p] Stephen B. Heitner, MD,[q] Daniel L. Jacoby, MD,[q] Stuart Kupfer, MD,[q] Fady I. Malik, MD, PhD,[q] Chiara Melloni, MD, MHS,[q] Lisa Meng, PhD,[q] Jenny Wei, PhD,[q] Mark V. Sherrid, MD,[r] Theodore P. Abraham, MD,[s] on behalf of the FOREST-HCM Investigators

ABSTRACT

BACKGROUND Standard-of-care (SoC) medications for the treatment of obstructive hypertrophic cardiomyopathy (oHCM) are recommended as first-line therapy despite the lack of evidence from controlled clinical trials and well known off-target side effects.

OBJECTIVES We describe the impact of SoC therapy downtitration and withdrawal in patients already receiving aficamten in FOREST-HCM (Follow-Up, Open-Label, Research Evaluation of Sustained Treatment with Aficamten in Hypertrophic Cardiomyopathy; NCT04848506).

METHODS Patients receiving SoC therapy (beta-blocker, nondihydropyridine calcium-channel blocker, and/or disopyramide) were eligible for protocol-guided SoC downtitration and withdrawal at the discretion of the investigator and after achieving a stable dose of aficamten for ≥4 weeks. Successful SoC withdrawal was defined as at least a 50% dose-reduction in ≥1 medication. Adverse events (AEs) were prospectively evaluated 1 to 2 weeks after any SoC withdrawal.

RESULTS Of 145 patients with oHCM who were followed for at least 24 weeks (mean age 60.5 ± 13.2 years; 44.8% female; 42% NYHA functional class III), 136 (93.8%) were receiving ≥1 SoC therapy; of those, 64 (47%) had an attempt at withdrawal, with 59 (92.2%) successful. Thirty-eight (64.4%) patients completely discontinued ≥1 medication, and 27 (45.8%) achieved aficamten monotherapy with 2 later restarting a SoC medication. There were no significant differences in baseline characteristics on day 1 in FOREST-HCM in those with a SoC-withdrawal vs no-withdrawal attempt. In patients who underwent successful SoC therapy withdrawal, NYHA functional class improved by ≥1 class in 79.2% from baseline, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score improved to 83.0 ± 15.8 points, and resting and Valsalva left ventricular outflow tract gradient improved to 14.3 ± 10.9 and 32.9 ± 21.4 mm Hg, respectively. N-terminal pro-B-type natriuretic peptide levels improved to a median of 220.0 pg/mL (Q1-Q3: 102.0-554.0.0 pg/mL) and high-sensitivity troponin I improved to a median of 6.0 ng/L (Q1-Q3:3.5-10.7 ng/L). Downtitration and withdrawal of SoC therapy did not impact these results (all *P* values for change were >0.05), and these changes were similar in patients who did not undergo SoC therapy withdrawal. There were no serious AEs attributed to SoC withdrawal and treatment emergent AEs were similar between groups.

CONCLUSIONS In FOREST-HCM, one-half of the patients with oHCM attempted downtitration and withdrawal of SoC medications while receiving aficamten treatment, with infrequent instances of resumption of SoC. Stopping and dose reduction of SoC medications were well tolerated with no adverse consequences in clinical measures of efficacy (Follow-Up, Open-Label, Research Evaluation of Sustained Treatment with Aficamten in Hypertrophic Cardiomyopathy [FOREST-HCM]; NCT04848506) (JACC. 2024;84:1839-1849) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

BB = beta-blockers

CCB = calcium-channel blockers

CMI = cardiac myosin inhibitor

HCM = hypertrophic cardiomyopathy

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

LVOT-G = left ventricular outflow tract gradient

SoC = standard of care

Standard-of-care (SoC) treatment for patients with obstructive hypertrophic cardiomyopathy (oHCM) includes beta-blockers (BBs), nondihydropyridine calcium-channel blockers (CCBs), and disopyramide. SoC medications are currently recommended as first- and second-line therapy in patients with symptomatic oHCM to improve quality of life and symptoms, but they do not selectively target the underlying pathobiology of oHCM and can have unwanted off-target effects including bradycardia, chronotropic incompetence, erectile dysfunction, depression, leg edema, constipation, and anticholinergic side effects.[1,2] SoC therapies can also be useful in managing hypertension, palpitations, and some of the arrhythmias that might occur in the setting of oHCM. In the first randomized crossover study in oHCM, metoprolol improved left ventricular outflow tract gradients (LVOT-Gs) and symptoms but had a minimal effect on Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score (+2.4 points) and no effect on peak oxygen consumption or N-terminal pro-B-type natriuretic peptide (NT-proBNP).[3] Furthermore, in a study in patients with heart failure with preserved ejection fraction, withdrawal of metoprolol resulted in improvement in peak oxygen consumption during exercise and patient reported outcomes.[4]

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Aficamten is a next-in-class cardiac myosin inhibitor (CMI) which normalizes the myocardial hypercontractility characteristic of oHCM. Aficamten was evaluated in symptomatic patients with oHCM on SoC treatment in the REDWOOD-HCM (Randomized Evaluation of Dosing With CK-3773274 in Obstructive Outflow Disease in HCM; NCT04219826) and SEQUOIA-HCM (Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; NCT05186818) trials. Aficamten therapy appeared safe and effective in improving exercise capacity, symptoms, health status, LVOT-G, and cardiac biomarkers.[5-8] Patients who successfully completed one of these trials for aficamten were invited to rollover into FOREST-HCM (Follow-up Open-label, Research Evaluation of Sustained Treatment of Aficamten in HCM; NCT04848506).

The completed clinical trials of aficamten have recruited patients who remain symptomatic despite SoC therapies and subsequently randomized them against placebo or enrolled into an open-label trial. This strategy is based on evaluating incremental efficacy of CMIs and is driven by contemporary societal consensus guidelines.[1,9] As such, the potential clinical benefits of SoC therapies have presented a challenge to randomizing patients to placebo off SoC for the duration of the clinical trial.[9] REDWOOD-HCM (cohorts 1-3) and SEQUOIA-HCM recruited symptomatic patients on a combination of any of the guideline-recommended therapies for oHCM, including those unable to tolerate any SoC therapies.[5-7] Patients from these trials were eligible to enroll in an open-label trial, FOREST-HCM. Given the sizable treatment effect of aficamten, and the potential adverse effects (AEs) of SoC, it was believed that, within FOREST-HCM, it would be appropriate to allow for the withdrawal of SoC once titration of aficamten was complete. Our aim was to assess the safety and impact on hemodynamics and symptoms of downtitration and withdrawal of SoC therapies while receiving aficamten as well as to evaluate aficamten as a potential monotherapy in patients with oHCM.

From the [a]Oregon Health and Science University, Portland, Oregon, USA; [b]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [c]Complexo Hospitalario Universitario A Coruña, INIBIC, CIBERCV-ISCIII, A Coruña, Spain; [d]Barts Heart Centre and University College London, London, United Kingdom; [e]Lahey Hospital and Medical Center, Burlington, Massachusetts, USA; [f]Saint Luke's Mid America Heart Institute, Kansas City, Missouri, USA; [g]National Institute of Cardiology, Warsaw, Poland; [h]University of Pennsylvania, Philadelphia, Pennsylvania, USA; [i]University of Michigan Medical Center, Ann Arbor, Michigan, USA; [j]Massachusetts General Hospital, Boston, Massachusetts, USA; [k]Cedars-Sinai Medical Center, Los Angeles, California, USA; [l]Hospital Universitario Puerta de Hierro de Majadahonda, IDIPHISA, CIBERCV, Madrid, Spain; [m]Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain; [n]Meyer Children's Hospital, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Florence, Italy; [o]Section of Cardiology, Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas, USA; [p]Duke Cardiology Duke University Hospital, Durham, North Carolina, USA; [q]Cytokinetics, Incorporated, South San Francisco, California, USA; [r]Leon H. Charney Division of Cardiology, NYU Langone Health, New York, New York, USA; and the [s]University of California-San Francisco, San Francisco, California, USA.

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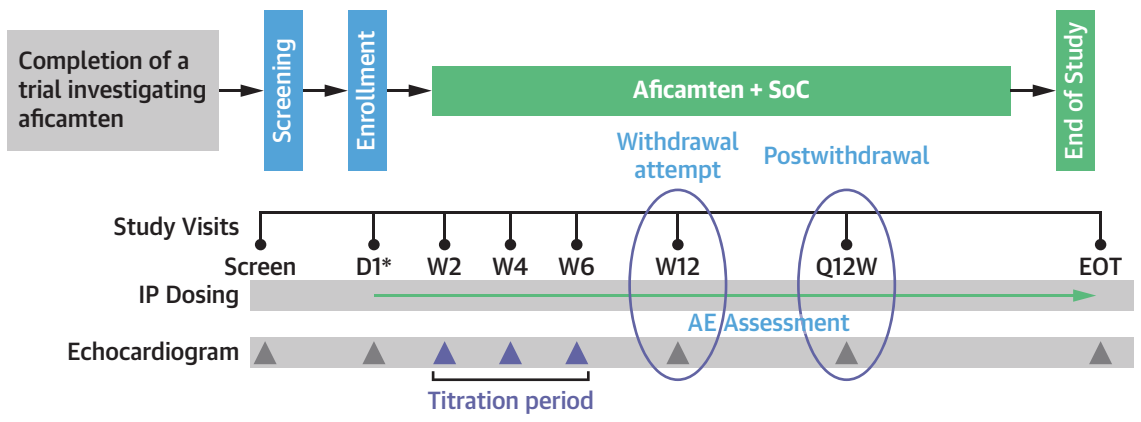
FIGURE 1 Trial Design



Schema of the FOREST-HCM (Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Aficamten in Adults With HCM) trial, modified to represent standard-of-care (SoC) therapy withdrawal timeline and assessments. Withdrawal of SoC therapies was typically done as allowed per protocol at 4 weeks after achieving a stable dose of aficamten. This period usually coincides with week (W) 12 on aficamten. Standardized adverse events (AEs) assessment was conducted 1-2 weeks after withdrawal. *Baseline characteristics. D = day; EOT = end of trial; IP = investigational product; Q = every.

METHODS

FOREST-HCM STUDY DESIGN. Patients with oHCM who completed a parent aficamten study were invited to enroll in FOREST-HCM. The design of REDWOOD-HCM and SEQUOIA-HCM have been previously published.[5,6,10] Patients enrolled in FOREST-HCM are required to have successfully completed a parent study with aficamten and have a left ventricular ejection fraction (LVEF) ≥55%. Site-read echocardiograms were used for aficamten titration, safety, and efficacy assessments (Figure 1). The study was approved at each participating site by a local or a central Institutional Review Board, all patients were provided written informed consent, and the study was performed in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines.

AFICAMTEN DOSE ADJUSTMENT. Aficamten was initiated at 5 mg orally once daily in all patients, and individualized dose selection was implemented by the treating physician after review of the echocardiogram. Dose adjustments were not forced and allowed for integration of clinical data (eg, symptoms) by the treating physician. Doses could be uptitrated in 5-mg increments approximately every 2 weeks to a maximum of 20 mg daily, with the intent of maintaining LVEF ≥50% and relieving LVOT obstruction (Valsalva LVOT-G ≤30 mm Hg) during the titration phase. The aficamten dose was reduced to the next lower dose if LVEF was 40% to <50% or temporarily interrupted if LVEF was <40% at any visit. If the LVEF was <50% before or at the week 2 visit, aficamten was to be permanently discontinued. To mirror clinical practice, dose adjustments were allowed at any time during the study, but a follow-up visit with an echocardiogram was required 2 weeks after dose adjustments.

SoC THERAPY DOWNTITRATION AND WITHDRAWAL. Per protocol, principal investigators (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 downtitration of SoC therapy and discontinuation was at the discretion of the PI. The aficamten dose could be escalated if the follow-up echocardiography met the appropriate per-protocol criteria (described above). Successful SoC therapy withdrawal was defined as dose reduction of ≥1 SoC medication by at least ≥50% from baseline. Patients had prespecified, per-protocol, safety follow-up (by phone or in person) 1 to 2 weeks after withdrawal or reduction of any SoC therapies. Only patients who had at least one clinical and echocardiographic assessment post SoC therapy withdrawal were included in this analysis. Other cardiovascular comorbidities with potential indication for SoC therapies were recorded, including coronary artery disease, hypertension, and atrial

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TABLE 1 Baseline Characteristics in the Overall Population and Stratified by SoC Medications Withdrawal

	All Patients on SoC (N = 136)	Patients With SoC Withdrawal Attempt (n = 64)	Patients Without SoC Withdrawal Attempt (n = 72)
Age, y	60.5 ± 13.2	60.5 ± 13.8	60.4 ± 12.7
Female	63 (46.3)	31 (48.4)	32 (44.4)
Race			
White	131 (96.3)	62 (96.9)	69 (95.8)
African American or Black	3 (2.2)	1 (1.6)	2 (2.8)
Asian	2 (1.5)	1 (1.6)	1 (1.4)
BMI, kg/m^2	29.4 ± 4.5	29.4 ± 4.3	29.4 ± 4.7
Atrial fibrillation or flutter	26 (19.1)	12 (18.8)	14 (19.4)
Syncope	21 (15.4)	13 (20.3)	8 (11.1)
Hypertension	57 (41.9)	24 (37.5)	33 (45.8)
Known HCM-causing gene mutation or positive family history	46 (33.8)	18 (28.1)	28 (38.9)
Heart rate, beats/min	62.5 ± 9.6	63.7 ± 11.1	61.4 ± 8.0
Systolic blood pressure, mm Hg	123.5 ± 15.7	123.9 ± 14.4	123.1 ± 16.8
Diastolic blood pressure, mm Hg	71.3 ± 11.4	71.1 ± 10.2	71.5 ± 12.3
NYHA functional class			
I	1 (0.7)	0 (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, points	71.0 ± 19.14	68.7 ± 19.71	73.0 ± 18.55
Beta-blocker	119 (87.5)	56 (87.5)	63 (87.5)
Calcium-channel blocker	29 (21.3)	13 (20.3)	16 (22.2)
Disopyramide	28 (20.6)	16 (25.0)	12 (16.7)
≥2 SoC medications	37 (27.2)	20 (31.3)	17 (23.6)
NT-proBNP, pg/mL	933.5 (387-1,874)	966 (387-1,643)	918.5 (382-1,946.5)
hs-cTnI, ng/L	12.2 (6.2-19.8)	11.0 (5.4-18.0)	12.5 (7.2-23.0)
LVEF,[a] %	67.9 ± 5.7	68.3 ± 5.8	67.6 ± 5.7
LVOT-G[a] at rest, mm Hg	57.8 ± 37.8	53.0 ± 34.0	61.9 ± 40.5
LVOT-G[a] at Valsalva, mm Hg	95.6 ± 39.3	94.0 ± 40.9	97.1 ± 38.2

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Site reported LVOT-G.

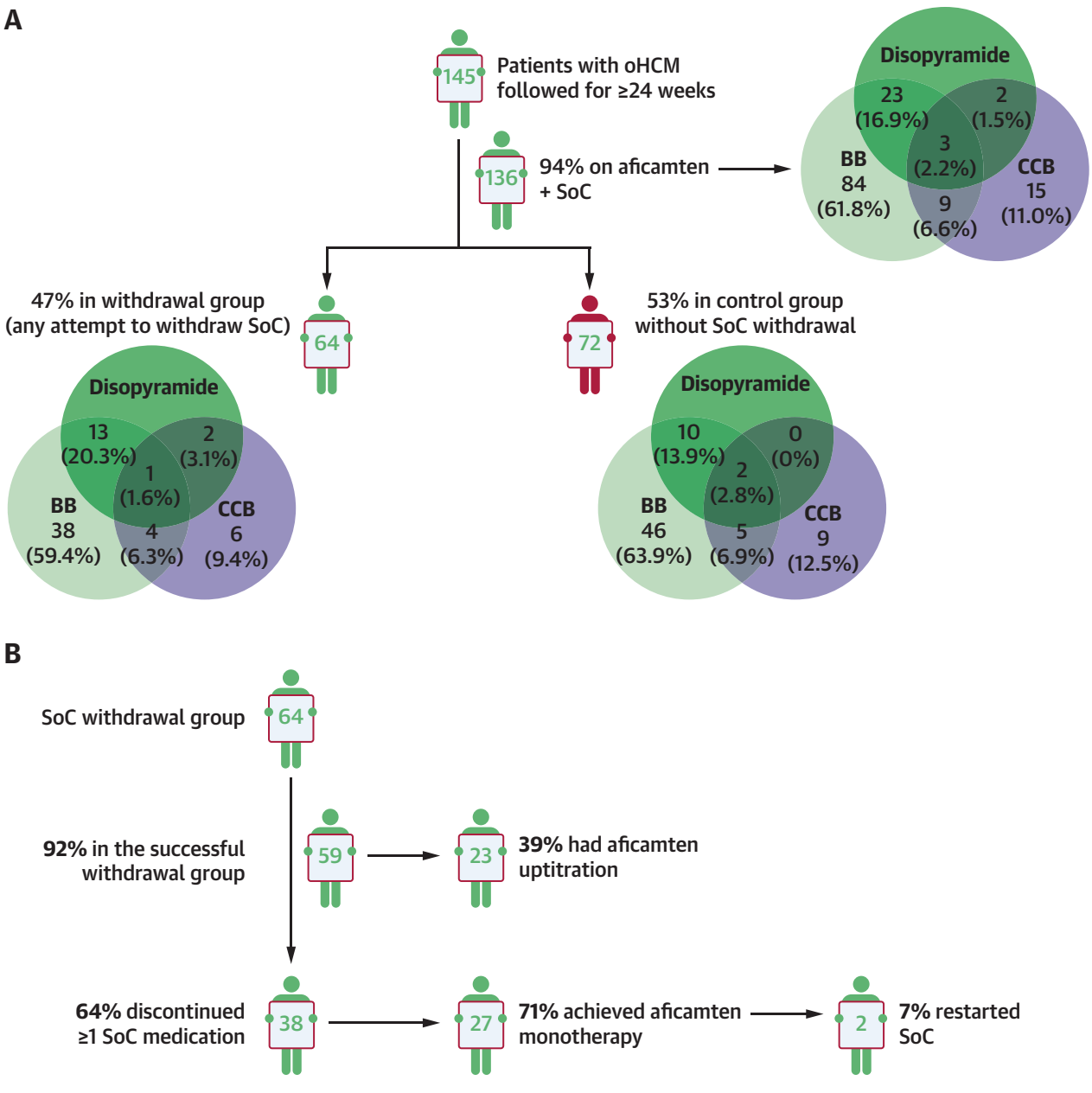
BMI = body mass index; HCM = hypertrophic cardiomyopathy; hs-cTnI = high-sensitivity cardiac troponin I; KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF = left ventricular ejection fraction; LVOT-G = left ventricular outflow tract gradient; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SoC = standard of care.

fibrillation. When clinically indicated and at the PIs discretion, SoC therapy was adjusted before achieving a stable dose of aficamten.

OUTCOMES. NYHA functional class, patient-reported health status (KCCQ-Clinical Summary Score [KCCQ-CSS]), LVOT-G at rest and with the Valsalva maneuver, and cardiac biomarkers (NT-proBNP and high-sensitivity cardiac troponin I [hs-cTnI]) were assessed at baseline and each study visit after the titration period (weeks 2-8, when echocardiographic-titration visits were conducted). Treatment-emergent AEs were collected at each visit.

STATISTICAL ANALYSIS. Baseline characteristics of patients attempting SoC therapy withdrawal were compared with those continuing SoC therapy. Because the decision to withdraw from SoC therapies occurred ad hoc during follow-up, baseline characteristics were not statistically compared. Change from baseline in efficacy outcomes was evaluated in patients with and without SoC therapy withdrawal attempt. An intention-to-treat paired analysis was performed of the safety and efficacy of successful SoC therapy withdrawal. A control group of patients who did not undergo SoC withdrawal was used to compare the safety and efficacy outcomes between the 2 groups. Preassessments and postassessments were chosen to mirror the timeline of SoC therapy withdrawal assessments. The treatment-emergent AEs were recorded throughout the duration of enrollment in the trial and for all subjects who received at least 1 dose of aficamten. Continuous variables were reported as mean ± SD or median (Q1-Q3), whereas categorical variables were presented as counts and percentages. Efficacy outcomes change from baseline were compared using 1-sample paired Student's *t*-test,

FIGURE 2 Patient Disposition



Disposition of patients enrolled in the FOREST-HCM trial according to (A) SoC withdrawal and (B) SoC withdrawal results. BB = beta-blocker; CCB = calcium channel blocker; oHCM = obstructive hypertrophic cardiomyopathy; other abbreviations as in Figure 1.

whereas in those undergoing SoC withdrawal, the 2-sample paired Student's *t*-test was used to compare pre- and post-SoC withdrawal measurements. The 2-sample paired Student's *t*-test was used to compare the difference of changes between the group of patients who had successful SoC therapy withdrawal and the group of patients who did not undergo SoC withdrawal. Statistical significance was established at $P < 0.05$. Statistical analysis was conducted using SAS Enterprise Guide, version 8.3 (SAS Institute, Inc).

TABLE 2 Paired Analysis of the Outcomes at Baseline (Day 1 of Aficamten), Before, and After Successful SoC Withdrawal

	Successful SoC Withdrawal Group (n = 59)				No Soc Withdrawal Group (n = 72)				Between Group
	Baseline	Pre /Week 12	Post	*P* Value[a]	Baseline	Week 12[b]	Week 24[b]	*P* Value[c]	*P* Value[d]
Symptoms									
NYHA functional class, ≥1 improvement, %		79.2	83.0	0.75		75.0	76.5	1.0	0.70
KCCQ CSS, points	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, beats/min	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 blood pressure, mm Hg	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 blood pressure, mm Hg	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,[e] %	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[e] at rest, mm Hg	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[e] at Valsalva, mm Hg	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	851 (346-1,498)	220 (102.0-554)	186 (72.0-475)	0.81	918.5 (382-1,946.5)	191.5 (78.0- 531.0)	167.5 (76.0-376.0)	0.75	0.96
hs-TnI, ng/L	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

Values are mean ± SD or median (Q1-Q3), unless otherwise indicated. [a]*P* value comparing pre-withdrawal and postwithdrawal. [b]Preassessments and postassessments were chosen to mirror the timeline of SoC therapy withdrawal assessments. [c]*P* value comparing week-12 and week-24 assessments. [d]*P* value comparing change in the SoC successful withdrawal cohort vs change in controls (no SoC withdrawal). [e]Site-read echo results.

Abbreviations as in Table 1.

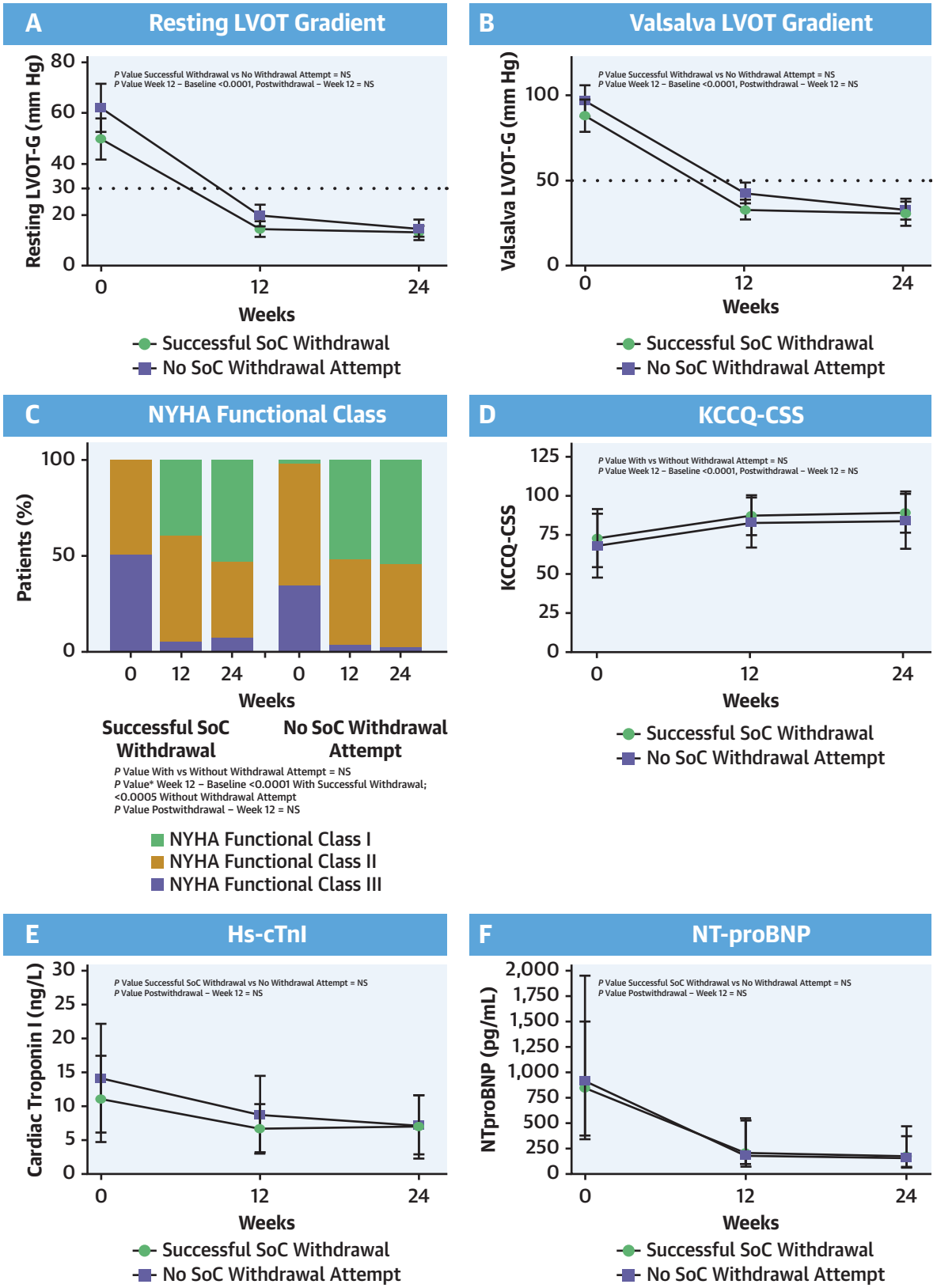
RESULTS

From May 28, 2021, to February 15, 2024, 145 patients with oHCM enrolled in FOREST-HCM who had been followed for ≥24 weeks were included in the analyses. Of these, 136 (93.8%) patients were receiving ≥1 SoC therapy: BB (n = 84 [61.8%]), CCB (n = 15 [11.0%]), BB + CCB (n = 9 [6.6%]), BB + disopyramide (n = 23 [16.9%]), CCB + disopyramide (n = 2 [1.5%]), and/or BB + CCB + disopyramide (n = 3 [2.2%]) and were eligible for SoC therapy withdrawal. There were no significant differences in baseline characteristics between patients attempting SoC withdrawal vs those who did not (Table 1). Of the 136 patients, 64 (47%) underwent a withdrawal attempt, and of those 59 (92.2%) achieved successful withdrawal (Figure 2A). There were no clear reasons reported for failure of SoC withdrawal in 4 patients, and in the fifth patient, bisoprolol was increased again for chest pain during follow-up. Thirty-eight (64.4%) patients completely discontinued ≥1 SoC medication, and 27 (45.8%) achieved aficamten as monotherapy with 2 monotherapy patients later restarting ≥1 SoC medication at the site PI's discretion (1 for hypertension and 1 for hypertrophic cardiomyopathy [HCM]) (Figure 2B). Twenty-eight (20.6%) of 136 patients were receiving disopyramide at the time of study enrollment and, of these patients, 16 attempted withdrawal, with 14 successfully discontinuing disopyramide. Details of type and dosages of SoC medications before and after withdrawal are shown in Supplemental Table 1.

ASSESSMENT OF CLINICAL RESPONSE TO SoC THERAPY WITHDRAWAL. To evaluate the clinical response to SoC therapy withdrawal, a pre-SoC and post-SoC withdrawal paired analysis was performed on 59 patients (92.2%).

HEMODYNAMIC RESPONSE. After SoC withdrawal, there was a significant increase in mean resting heart rate from 66.0 ± 12.8 beats/min to 70.7 ± 11.0 beats/min ($P < 0.002$), whereas the heart rate decreased slightly in patients who did not undergo SoC withdrawal (from 64.7 ± 9.1 beats/min to 62.1 ± 8.5 beats/min, $P = 0.005$). There were no significant effects of SoC withdrawal on systolic and diastolic blood pressure (Table 2). However, 3 patients were initiated on amlodipine and 1 patient on olmesartan for blood pressure management after withdrawal. The mean baseline resting and Valsalva LVOT-G (site-reported) in patients attempting SoC therapy withdrawal were 49.8 ± 29.2 mm Hg and 88.3 ± 34.2 mm Hg, respectively, and decreased to 14.3 ± 10.9 mm Hg and 32.9 ± 21.4 mm Hg (change from baseline $P < 0.0001$ for both) before SoC withdrawal. The mean change (95% CI) in rest and Valsalva LVOT-G following SoC withdrawal was -1.8 mm Hg (95% CI: -5.4 to 1.8; $P = 0.32$) and -2.5 mm Hg (95% CI: -11.0 to 6.0; $P = 0.56$), respectively, and the absolute mean

FIGURE 3 Efficacy Outcomes



Efficacy of aficamten in the SoC withdrawal group vs no withdrawal group during follow-up. (A) Resting left ventricular outflow tract (LVOT) gradient. (B) Valsalva left ventricular outflow tract gradient (LVOT-G). (C) Proportion of patients in different NYHA functional class. (D) Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS). (E) N-terminal pro-B-type natriuretic peptide (NT-proBNP). (F) High-sensitivity cardiac troponin I (hs-cTnI). *Proportion of patients with ≥1 class improvement in NYHA functional class. NS = not significant.

TABLE 3 Treatment Emergent Adverse Events

	SoC Therapy Withdrawal Attempt (n = 64)	No SoC Therapy Withdrawal Attempt (n = 72)
Duration of follow-up, days	354 (252.5-772.0)	271.0 (212.5-335.5)
Patients with ≥1 TEAE	47 (73.4)	50 (69.4)
Patients with TESAEs	12 (18.8)	6 (8.3)
Patients with fatal TEAEs	0 (0)	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)
LVEF <50% with clinical heart failure	0 (0)	0 (0)
Atrial fibrillation or flutter	5 (7.8)	3 (4.2)
New onset	1 (1.6)	0 (0)
Recurrent	4 (6.3)	3 (4.2)
With concurrent LVEF <50%	1 (1.5)	0 (0)

Values are median (Q1-Q3) or n (%).
AE = adverse event; TEAE = treatment-emergent adverse events; TESAE = treatment-emergent serious adverse events; other abbreviations as in Table 1.

values remained <50 mm Hg, the diagnostic threshold for significant LVOT obstruction. When comparing the impact of SoC withdrawal on hemodynamics to the patients who did not undergo SoC withdrawal attempt over a similar time interval, there were no significant differences observed (resting LVOT-G $P = 0.19$ and Valsalva LVOT-G $P = 0.17$) (Figures 3A and 3B). Aficamten uptitration during follow-up (ie, after the post-SoC withdrawal assessment) occurred in 23 of 59 (39.0%) patients after SoC withdrawal, including 8 patients who achieved aficamten monotherapy.

SYMPTOMS AND PATIENT-REPORTED OUTCOMES. Baseline NYHA functional class and KCCQ-CSS are shown in Table 1. Pre-SoC withdrawal, aficamten resulted in improvement by ≥1 NYHA functional class in 79.2% of patients (change from baseline $P < 0.0001$), and improvement in KCCQ-CSS from 69.1 ± 20.4 points to 83.0 ± 15.8 points ($P < 0.0001$ for change from baseline). Post-SoC withdrawal, there was no change in either the proportion of subjects achieving ≥1 NYHA functional class improvement ($P = 0.75$) or change in KCCQ-CSS ($P = 0.43$) (Table 2). When post-SoC withdrawal changes were compared with the no-SoC withdrawal group, there were no differences for either endpoint ($P = 0.70$ and $P = 0.98$, respectively) (Table 2, Figures 3C and 3D).

CARDIAC BIOMARKERS. Pre-SoC withdrawal, aficamten treatment resulted in a reduction in median change of both NT-proBNP and hs-cTnI from 851 pg/mL (Q1-Q3: 346.0-1,498.0 pg/mL) and 10.7 ng/L (Q1-Q3: 5.1-17.9 ng/L) to 220 pg/mL (Q1-Q3: 102.0-554.0 pg/mL) and 6.0 ng/L (Q1-Q3: 3.5-10.7 ng/L), respectively (both $P < 0.001$). After SoC withdrawal, both NT-proBNP ($P = 0.81$) and hs-cTnI ($P = 1.00$) remained stable. When these changes were compared to the non-SoC withdrawal group, there was no difference for either biomarker (Table 2, Figures 3E and 3F).

SENSITIVITY ANALYSIS. A sensitivity analysis of all the efficacy assessments shown in Table 2 was performed excluding any patient with any change to SoC therapies before week 12. Results are presented in Supplemental Table 2 and were similar to the results shown in the overall cohort.

AFICAMTEN MONOTHERAPY. A total of 27 patients successfully discontinued all SoC therapies and remained on aficamten monotherapy. The safety and efficacy outcomes in these patients were similar compared with the overall group who underwent SoC withdrawal attempt.

SAFETY. Among patients attempting SoC therapy withdrawal, no serious AEs attributable to withdrawal were reported. Treatment-emergent AEs reported over the whole duration of enrollment were comparable between patients attempting withdrawal and those who did not, as detailed in Table 3 and Supplemental Table 3. Mean site-reported LVEF was 69.0% ± 5.4% at baseline, 65.9% ± 6.1% pre-SoC withdrawal, and 65.0% ± 6.2% post-SoC withdrawal. Mean LVEF differences between SoC withdrawal and no-withdrawal groups were similar ($P = 0.77$) (Table 2). Three patients showed an LVEF <50% in the SoC withdrawal group, and 2 in the no-withdrawal group, with none associated with SoC withdrawal. One of these site-read LVEF values <50% was corroborated by the core laboratory, and all 5 patients underwent dose reductions, with return of their LVEF to >50%. None of the patients had clinical heart failure. New-onset atrial fibrillation and flutter were uncommon, occurring in 1 patient (Table 3).

LONGER-TERM FOLLOW-UP. Among patients attempting SoC withdrawal, the median follow-up duration from enrollment was 354 days (Q1-Q3: 252.5-772.0 days) and the median follow-up post-SoC withdrawal was 271 days (Q1-Q3: 147-699 days), encompassing a total of 306 visits over 132 weeks postwithdrawal. Ongoing monitoring revealed sustained tolerability and efficacy after SoC withdrawal.

DISCUSSION

We have shown that patients in FOREST-HCM were frequently and safely able to undergo successful withdrawal of SoC medications after initiation of

aficamten without negatively impacting hemodynamics, symptoms, or cardiac biomarkers. The treatment effect of aficamten was not clinically meaningfully different in patients who underwent SoC withdrawal when compared with patients who did not undergo SoC withdrawal. Understanding the limitation that this was conducted in an open-label fashion without the benefits of randomization, this implies that combination therapy in oHCM may not impart additional advantages over monotherapy. This finding may ultimately help minimize polypharmacy and associated risks and side effects in these patients.

The current study represents the first-ever attempt to evaluate the safety and efficacy of withdrawing SoC therapy in a CMI trial. FOREST-HCM is specifically designed to mimic real-world clinical decision making, where investigators are enabled independently to incorporate components of the clinical picture, patient preference, and medical need, both when considering the dose selection of aficamten (based on echocardiographic parameters) and regarding alteration of SoC therapies. Although there is guidance within the protocol that indicates a strategy for SoC therapy withdrawal, the decisions on how to achieve this was ultimately made according to the clinical discretion of the site PI. Eighteen patients initiated SoC withdrawal before achieving a stable dose of aficamten, suggesting that the per-protocol guidance may represent a more conservative approach. Importantly, the protocol required systematic evaluation of patients after SoC withdrawal and enables rigorous assessment of the safety of such an approach.

The first-line therapy for patients with oHCM are BBs, with their use dating back to the 1960s and with the first randomized crossover trial of metoprolol having shown improvement in LVOT-G and symptoms but no effect on exercise capacity or NT-proBNP.[3,11] BBs target the β1-adrenergic receptors in the myocardium leading to heart rate reduction and negative inotropic effect. BBs, even those designated as cardiac specific, are associated with frequent extracardiac side-effects including mood disturbances, weight gain, fatigue, and erectile dysfunction.[12] BBs may also decrease functional capacity through chronotropic incompetence and reduction of peak oxygen uptake, a heart-rate dependent measure.[4] Nondihydropyridine CCBs (eg, diltiazem and verapamil) inhibit the calcium ion influx through slow channels in the myocardial cells leading to heart rate reduction and slowing atrioventricular conduction with mild negative inotropic effects.[13] CCBs are associated with extracardiac side effects, including constipation and ankle swelling. Importantly, CCB initiation is associated with the potential to paradoxically increase LVOT obstruction because of peripheral vasodilation and reduction of afterload. Disopyramide is a Class Ia antiarrhythmic agent that targets multiple ion channels, lowering calcium transients and force generation, leading to reduction in LVOT obstruction.[14] Disopyramide has numerous extracardiac anticholinergic side effects, including dry eyes, dry mouth, constipation, bloating, urinary retention, it can rarely be proarrhythmogenic, and it is associated with tachyphylaxis. Disopyramide is consequently contraindicated in patients with glaucoma, known urinary retention, and myasthenia gravis.[15] Importantly, none of these medications directly target the underlying pathophysiology of oHCM and are used predominantly due to their off-target reduction of cardiac contractility.

Aficamten directly targets the hypercontractility underlying HCM with a modest effect on LVEF. Aficamten does not directly affect heart rate, cardiomyocyte calcium transients, or neurohormonal pathways involved in cardiac contractility. As such, aficamten appears to be well tolerated and not associated with significant extracardiac side effects.[5-7] This report shows that: 1) efficacy from aficamten is maintained even after withdrawal of SoC therapy in close to one-half of the patients enrolled in FOREST-HCM; and 2) downtitration and withdrawal was not associated with safety concerns, including without the development of new or worsening clinical arrhythmic events. Although some patients might have an increase in their LVOT-G with removal of any of these negative inotropes, the change in LVOT-G was mostly minimal and, if deemed clinically significant and associated with symptoms, uptitrating the aficamten dose would address this. Aficamten uptitration occurred in 39% of patients who underwent SoC withdrawal at the discretion of the PI and following protocol guidance. An important observation that supports the maintenance of the overall treatment effect of aficamten independent from SoC therapies, despite the lack of randomization, is that NT-proBNP, a biomarker of increased wall stress and adverse outcomes in HCM, was not negatively impacted by the withdrawal of SoC therapies.[16-18]

The withdrawal of SoC did not impact the observed benefit of aficamten on NYHA functional class and KCCQ-CSS. Reduction in the burden of pharmacotherapy and potential side effects is expected to have a favorable impact on quality of life. However, the KCCQ-CSS tool is not designed to specifically assess these aspects of withdrawal of SoC therapies in patients with oHCM, and a larger sample size with a longer-term follow-up might be required to see an effect on quality of life.

The absence of controlled studies supporting the use of SoC therapies in oHCM combined with these data from FOREST-HCM strongly support the research questions being asked in MAPLE-HCM (Metoprolol vs Aficamten in Patients with LVOT Obstruction on Exercise Capacity in HCM; NCT05767346), the ongoing phase 3 trial of aficamten versus metoprolol in patients with symptomatic oHCM. This study will hopefully generate the evidence needed to ascribe either aficamten or metoprolol as a first-line therapy in oHCM, as well as provide the controlled data necessary to independently evaluate each treatment effect on exercise capacity, symptoms, and measures of cardiac remodeling. Furthermore, MAPLE-HCM will specifically address aficamten's efficacy as frontline monotherapy in oHCM.

STUDY LIMITATIONS. First, the data are observational and nonrandomized, with the comparators for SoC withdrawal being patients within FOREST-HCM who did not undergo SoC withdrawal and, although there were no significant differences between groups by baseline characteristics, this does not represent true randomization. By design, site PIs were allowed to adjust aficamten and SoC therapies according to the clinical needs of the patient and were not bound by the aficamten titration algorithm nor by the SoC withdrawal guidance. With the implementation of investigator autonomy, some structured analyses are more difficult; however, this feature of FOREST-HCM does give insights into future practice if aficamten achieves regulatory approval. Second, echocardiographic assessments after SoC withdrawal occurred approximately 12 weeks later, and acute hemodynamic effects of SoC withdrawal may have been missed. However, patients received a phone call from sites 1 to 2 weeks after SoC withdrawal and, in cases where significant hemodynamic rebound from SoC withdrawal was observed, this did not rise to the level of clinical significance (AEs or clinic visits).

CONCLUSIONS

Patients with oHCM in FOREST-HCM frequently underwent successful downtitration and withdrawal of SoC medications while on aficamten treatment without negatively impacting hemodynamics, symptoms or cardiac biomarkers. Further, the treatment effect of aficamten was not clinically different in patients who underwent SoC withdrawal compared with patients who did not undergo SoC withdrawal. Further study of aficamten as a first-line monotherapy in patients with oHCM is ongoing in the MAPLE-HCM trial.

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ADDRESS FOR CORRESPONDENCE: Dr Ahmad Masri, Hypertrophic Cardiomyopathy Center, Knight Cardiovascular Institute, Oregon Health and Science University, Mail code: UHN-62, 3181 SW Sam Jackson Road, Portland, Oregon 97239, USA. E-mail: masria@ohsu.edu. X handle: @MasriAhmadMD.

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APPENDIX For supplemental tables, please see the online version of this paper.