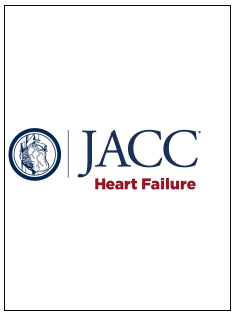

Concomitant Aficamten and Disopyramide in Symptomatic Obstructive Hypertrophic Cardiomyopathy

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Concomitant Aficamten and Disopyramide in Symptomatic Obstructive Hypertrophic Cardiomyopathy

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Data Availability Statement:

Qualified researchers may submit a request containing the research objectives, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Cytokinetics Inc. does not grant external requests for individual patient data for the purpose of reevaluating safety and efficacy issues already addressed in the product labeling. Requests are reviewed by a committee of internal advisors, and if not approved, may be further arbitrated by a Data Sharing Independent Review Panel. Upon approval, the information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Requests may be submitted to medicalaffairs@cytokinetics.com.

Abstract

Background: Disopyramide, used in obstructive hypertrophic cardiomyopathy (oHCM) for its negative inotropic properties mediated by its reduction in cytosolic calcium, has been recommended for decades as an option to relieve resistant obstruction. Aficamten is a selective cardiac myosin inhibitor that reduces hypercontractility directly by reducing myosin-actin interaction.

Objectives: Investigate safety and efficacy of concomitant use and withdrawal of disopyramide in patients with symptomatic oHCM receiving aficamten.

Methods*:* Patients with oHCM enrolled in REDWOOD-HCM Cohort 3 (open-label), SEQUOIA-HCM (placebo-controlled), and FOREST-HCM (open-label) were analyzed. We identified 4 groups, each with patients symptomatic despite background therapy with disopyramide who received: (1) disopyramide plus aficamten and subsequent aficamten withdrawal per protocol (Diso-Afi Withdrawal); (2) disopyramide plus placebo (Diso-Pbo); (3) aficamten plus disopyramide with subsequent disopyramide withdrawal (Afi-Diso Withdrawal); (4) continued both disopyramide and aficamten (Diso+Afi Continuous). Assessments were performed at baseline, after aficamten or placebo add-on therapy, and after washout (except at week 24 for Diso+Afi Continuous group).

Results: Overall, 50 unique patients from 3 trials enrolled, resulting in 93 subjects (segments) across 4 groups: Diso-Afi Withdrawal, (n=29), Diso-Pbo (n=20), Afi-Diso Withdrawal (n=17), and Diso+Afi Continuous (n=27); mean disopyramide dose was 331±146 mg/day. The addition of aficamten to disopyramide alleviated left ventricular outflow tract (LVOT) obstruction (resting: change [Δ] in least squares mean [LSM]±SD –27.0±3.6, Valsalva: Δ LSM±SD –39.2±5.0, both p<0.0001), symptoms (≥1 NYHA class improvement: 77.8% [95% CI 61.0, 94.5,

p<0.0001], KCCQ-CSS(mean ±SD): 12.3±3.3 [p<0.001]), and reduced NT-proBNP ratio: 0.35 (95% CI 0.26, 0.48, p<0.0001), while no significant change with placebo. Withdrawal of aficamten while on disopyramide resulted in return of LVOT obstruction, worsening of symptoms, and increase in NT-proBNP to baseline values. Conversely, withdrawal of disopyramide while on aficamten did not impact efficacy. There were no safety events associated with aficamten or disopyramide withdrawal, and no episodes of atrial fibrillation after disopyramide withdrawal.

Conclusions: In this cohort of patients with symptomatic oHCM with persistent LVOT obstruction, combination therapy with aficamten and disopyramide was safe and well tolerated, but did not enhance clinical efficacy vs aficamten alone. For such oHCM patients, aficamten treatment may be considered with an option to discontinue disopyramide.

Clinical Trial Registration: https://clinicaltrials.gov/; Unique identifiers: NCT04219826 (REDWOOD-HCM); NCT05186818 (SEQUOIA-HCM); NCT04848506 (FOREST-HCM)

Key Words: aficamten, obstructive hypertrophic cardiomyopathy, disopyramide, left ventricular outflow tract gradient

Abbreviations and Acronyms:

BB, beta-blockers; CCB, calcium-channel blockers; CMI, cardiac myosin inhibitor; HCM, hypertrophic cardiomyopathy; hs-cTnI, high sensitivity troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association

INTRODUCTION

Medical management of obstructive hypertrophic cardiomyopathy (oHCM) is rapidly evolving. Beta blockers (BB) and non-dihydropyridine calcium channel blockers (CCB) remain the first line therapy in patients with symptomatic oHCM. The 2024 American College of Cardiology/American Heart Association (ACC/AHA) treatment guidelines recommend disopyramide as one of the second-line therapies in patients with oHCM who remain symptomatic (1). Leveraging its negative inotropic properties, the addition of disopyramide can effectively further lower left ventricular outflow (LVOT) gradients and improve limiting symptoms in some patients with oHCM, providing an important medical option for these patients. Disopyramide has a long track record having been used in this capacity for more than 4 decades (2-6) leading to a class I recommendation for it use in AHA/ACC and European guidelines. However, tachyphylaxis and anti-cholinergic side effects may limit its long-term use in a some patients, as well as a small pro-arrhythmic risk that requires QT interval monitoring Other second-line therapies recommended by the guidelines include cardi(6)ac myosin inhibitors (CMI) and septal reduction therapies (SRT)(1).

Aficamten is a next-in-class CMI, which has been demonstrated to be safe and effective in SEQUOIA-HCM (NCT05186818) for the treatment of symptomatic oHCM (7). Unlike BBs, CCBs and disopyramide, aficamten directly targets the underlying pathologic hypercontractility at the sarcomere level and without known off-target effects. Aficamten has been evaluated in patients with oHCM and persistent symptoms despite receiving background standard of care medical therapy, including disopyramide (REDWOOD-HCM Cohort 3 and SEQUOIA-HCM)(7,8). FOREST-HCM (NCT04848506) is a long-term extension study offered to patients completing a parent aficamten study and allows for the management of medical therapies (dose

adjustment, continuation or discontinuation) at the discretion of the local investigator.

EXPLORER-HCM (NCT03470545) evaluated the use of mavacamten, the first-in-class cardiac myosin inhibitor, in patients with symptomatic oHCM, but excluded patients receiving disopyramide(9). VALOR-HCM (NCT04349072) evaluated the use of mavacamten in patients identified to be candidates for SRT, and included a small group of patients receiving disopyramide, however data specific to those patients have yet to be reported (10). MAPLE-HCM (NCT05767346), an ongoing head-to-head comparison study, is the first trial to evaluate the safety and efficacy of current standard-of-care (metoprolol) against a myosin inhibitor (aficamten); to date, there is not a similar trial for disopyramide (11). Through the prospective collection of high-density and clinically relevant data, the aficamten development program thus presents a unique opportunity to evaluate the relevant outcome measures for patients already receiving dual-background therapy with an atrioventricular nodal blocker (BB, CCB) and disopyramide. These data allow for analyses of important potential treatment scenarios that could be encountered in the clinical setting including: combination with aficamten as triple-therapy; withdrawal of disopyramide after starting therapy with aficamten; stopping aficamten while continuing disopyramide; and treatment with disopyramide without adding aficamten (placebo) (Figure 1). Importantly, the patients included in aficamten trials were selected on the basis of continued limiting symptoms due to persistent left ventricular outflow tract (LVOT) obstruction at the time of enrollment and therefore may not represent those patients who demonstrate long-term and complete response with the addition of disopyramide only, as shown in a recent series. (4)

METHODS

Patients with persistent symptomatic oHCM (New York Heart Association [NYHA]

functional class ≥ II; LVOT gradients of ³30 mmHg at rest and/or ³50 mmHg with Valsalva) who were receiving disopyramide in addition to either BB or CCB, all at doses at the discretion of their treating physicians, and enrolled in REDWOOD-HCM Cohort 3 (open-label, NCT04219826), SEQUOIA-HCM (placebo-controlled, NCT05186818), or FOREST-HCM (open-label, NCT04848506) were included in this analysis. Patients had to meet the specific eligibility criteria for each trial to qualify. Additional criteria for inclusion in the analysis included the availability of serial clinical, echocardiographic, electrocardiographic, and biomarker assessments during the conduct of each trial (see definitions of the time-points below). Each study was approved at each participating site by a local or a central institutional review board, all patients provided written informed consent, and the studies were performed in accordance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines.

REDWOOD-HCM Cohort 3 Trial

The design and main results of the REDWOOD-HCM trial have been previously published (12). Briefly, patients with symptomatic oHCM with persistent significant LVOT obstruction (resting gradient ≥ 30 mmHg or Valsalva ≥ 50 mmHg) despite chronic disopyramide treatment were enrolled in this open-label 10-week trial of aficamten. Patients were evaluated at baseline, weeks 2, 4, 6, and 10 while on aficamten, and at week 12 after withdrawal of aficamten, while disopyramide was continued throughout. At the end of the treatment period, patients discontinued aficamten per protocol without a taper.

SEQUOIA-HCM Trial

The design and main results of the SEQUOIA-HCM trial were previously published(7). Briefly, patients with symptomatic oHCM with persistent significant LVOT obstruction (resting

gradient ≥ 30 mmHg and Valsalva ≥ 50 mmHg) on stable background medical therapy individually optimized per local practice for oHCM (BB, CCB, and/or disopyramide) prior to enrollment, and with impaired peak oxygen consumption (≤ 90% of age- and sex-predicted) were randomized to aficamten or placebo for 24 weeks in a double-blind fashion. Patients were evaluated at baseline, weeks 2, 4, 6, 8 and every 4 weeks thereafter through 24 weeks of treatment. At the end of the treatment period, patients discontinued aficamten per protocol without a taper. Patients were also assessed 4 weeks after aficamten or placebo washout. Background medical therapy was stable and continued throughout the trial.

FOREST-HCM Trial

Patients who completed an aficamten parent study (e.g. REDWOOD-HCM or SEQUOIA-HCM) were invited to participate in this long-term open-label extension study. Patients were required to be on stable background medical therapy prior to enrollment, including those taking disopyramide. FOREST-HCM was designed to mirror real-world practice where the local site investigators choose aficamten doses based on the echocardiogram-based algorithm provided in the study protocol. Withdrawal of background medical therapy (including disopyramide) was permitted at the investigators' discretion once patients were receiving a stable dose of aficamten for at least 4 weeks (13). The manner in which disopyramide was discontinued was left up to the investigator's discretion as clinically indicated and tolerated by the patient. All patients were evaluated at baseline, during the titration phase (weeks 2, 4, and 6,) and maintenance period (week ≥12).

Definition of 4 Groups

Patients enrolled in the aforementioned trials comprised the 4 groups identified by treatment with disopyramide (Diso), aficamten (Afi), and/or placebo (Pbo) **(Figure 1)**.

(1) **Diso-Afi Withdrawal**: Patients on disopyramide enrolled in REDWOOD-HCM Cohort 3 and in SEQUOIA-HCM who received aficamten during that study, and underwent withdrawal of aficamten during the per-protocol washout period.

(2) **Diso-Pbo**: Patients on disopyramide enrolled in SEQUOIA-HCM who were randomized to the placebo arm.

(3) **Afi-Diso Withdrawal**: Patients enrolled in FOREST-HCM on disopyramide at baseline who received aficamten for at least 24 weeks, had assessments on disopyramide, aficamten plus disopyramide, and post-disopyramide withdrawal.

(4) **Diso+Afi Continuous**: Patients enrolled in FOREST-HCM on disopyramide at baseline, began treatment with aficamten, and continued to receive both treatments throughout. In this group the Week 24 per-protocol visit was chosen as the final assessment time point.

Assessments and timepoints (Figure 1):

At each timepoint, patients underwent comprehensive evaluations including symptoms (NYHA class and Kansas City Cardiomyopathy Questionnaire-Clinical Summary score [KCCQ-CSS]), electrocardiogram, echocardiogram (left ventricular ejection fraction [LVEF] and LVOT gradient), biomarkers (N-terminal Pro-B-Type Natriuretic Peptide [NT-proBNP] high sensitivity troponin I [hsTnI]), and safety assessments). Site-assessed LVEF and LVOT gradients were used for the analyses. Three main timepoints (T) were generated for these assessments **(Figure 1)**: (T1) Baseline (disopyramide only); or Day 1 in each respective trial; (T2) after an add-on therapy was completed (either aficamten or placebo); and (T3) after withdrawal of the treatment (aficamten, disopyramide or placebo), except in the Diso+Afi Continuous group, where no withdrawal was conducted and the Week 24 visit was used.

Statistical Analysis

Baseline characteristics were summarized and reported for each group. Statistical comparisons at baseline were not performed given patients were enrolled in clinical trials using similar entry criteria. Continuous variables were reported as mean ± standard deviation (SD) or median (1^{st} quartile, 3^{rd} quartile), whereas categorical variables were presented as counts and percentages. NT-proBNP and hsTnI were summarized using geometric mean and geometric percent coefficient of variation (% GeoCV). Within and across group comparisons for continuous variables were conducted using a mixed model repeated measures (MMRM) that included model terms of baseline value, time point, group, baseline value by time point, and time point by group. For NT-proBNP and hsTnI levels, the proportional change was calculated as the ratio of the value with add-on therapy relative to the baseline value, and the value at withdrawal relative to that with add-on therapy. The log-transformed proportional change was analyzed using MMRM. Adjustments for multiple comparisons were not performed. Statistical analysis was conducted using SAS Enterprise Guide (Version 8.3; SAS Institute, Cary, NC, USA).

Results

In REDWOOD-HCM Cohort 3, all 13 subjects (100%) were on disopyramide at baseline, while 36 subjects (15.2%, out of 236 in SEQUOIA excluding patients enrolled in China since they did not rollover to FOREST-HCM) and 44 subjects (14.8% in FOREST-HCM) were on disopyramide. A total of 50 unique patients met the eligibility criteria for this analysis, resulting in 93 patients (study segments) enrolled across the 3 studies, and were included in the 4 groups as follows: Diso-Afi Withdrawal (n=29), Diso-Pbo (n=20), Afi-Diso Withdrawal (n=17), and Diso+Afi Continuous (n=27), Figure 1. Overall, mean age ranged from 58 to 63 years, 46% of patients were female, and 88% were White. Additional baseline characteristics are shown in

Table 1. The mean daily dose of disopyramide was 331.3 ± 146 mg. All 50 patients were receiving disopyramide at baseline, and 1 patient started disopyramide between the parent study and enrollment in FOREST-HCM. In addition to disopyramide therapy, 45 (90%) patients were receiving a BB, and 6 (12%) were on a CCB. Patients had symptomatic oHCM, with 19 (38%) having severe symptoms (NYHA class III), consistent with their ongoing disease burden while on HCM background medical therapy. On electrocardiography, QRS duration and QT interval were prolonged. The LVEF demonstrated relative hypercontractility (mean LVEF range 68-70%) and there was severe obstruction (mean resting LVOT gradient range = 50-64 mmHg; mean Valsalva LVOT gradient range = 87 to 94 mmHg) in each of the 4 groups. NT-proBNP and hsTnI were abnormally elevated (**Table 1**).

Effect of adding aficamten vs placebo to disopyramide therapy and subsequent aficamten withdrawal

The addition of aficamten to disopyramide therapy resulted in significant improvements in LVOT gradients at rest (ΔLSM ±SD -27.0 ±3.6 mmHg; p<0.0001) and with Valsalva maneuver (ΔLSM -39.2±5.0 mmHg; p<0.0001) and without relevant reduction in LVEF (ΔLSM±SD -2.0% ±1.0, p=0.052) (**Central Illustration Panels A, B, and C**). Additionally, ≥ 1 NYHA functional class improvement occurred in 77.8% (95% CI 61.0, 94.5; p<0.0001), and KCCQ-CSS improved by 12.3 ±3.3 (p<0.001) with adding aficamten to disopyramide treatment (**Table 3, Central Illustration Panels D and E**). Cardiac biomarkers also demonstrated significant improvements, with a proportional reduction in serum NT-proBNP of 0.35 (95% CI, 0.26, 0.48, p <0.0001) and hsTnI of 0.74 (95% CI 0.63, 0.87; p <0.001) (**Supplemental Table 1 and Central Illustration Panel F**). Withdrawal of aficamten while receiving disopyramide resulted in worsening of obstruction (Δ LSM resting LVOT gradient = 44.1±7.4 mmHg;

p<0.0001; and Δ LSM Valsalva LVOT gradient= 65.5±9.4 mmHg; p<0.0001) (**Table 2, Central Illustration panels A and B**).

In comparison, there were no improvements in response to the addition or removal of placebo (**Table 2, Central Illustration Panel A-F**).

Effect of disopyramide withdrawal vs continuation in patients on maintenance aficamten

In FOREST-HCM, 44 patients were receiving disopyramide at baseline; of those 17 were withdrawn from disopyramide during follow-up (i.e., Afi-Diso Withdrawal) and 27 patients were not (i.e., Diso+Afi Continuous). The addition of aficamten resulted in significant reductions in resting and Valsalva LVOT gradient (**Table 2**). Aficamten also resulted in significant improvement in NYHA functional class ≥1 in 13/16 patients in Afi-Diso Withdrawal (81.3%) (95% CI 59.8, 100.0; p=0.0001) and in 20/27 (74.1%) patients in Diso+Afi Continuous (95% CI 56.4, 91.7; p<0.0001) (**Central Illustration Panel C**). Aficamten significantly improved KCCQ-CSS (Δ LSM 10.4 ±3.3; p=0.003) in the Afi-Diso Withdrawal and Diso+Afi Continuous (Δ LSM 16.1 ±2.5; p<0.0001) groups (**Table 3, Central Illustration Panels A-E)**.

In the Afi-Diso Withdrawal group, withdrawal of disopyramide did not impact the hemodynamic benefits initially seen with the addition of aficamten (Δ LSM resting LVOT gradient = 3.0±8.9 mmHg, p=0.74; and Δ LSM Valsalva LVOT gradient = 8.2±11.2 mmHg, p=0.49), nor was there worsening of symptoms by NYHA class or KCCQ-CSS (Δ LSM KCCQ-CSS = 1.5 ±3.9; p=0.70), (**Tables 2 and 3, Central Illustration Panels A-E)**. In addition, withdrawal of disopyramide did not affect NT-proBNP (proportional change 0.75 [95%CI 0.52, 1.07]; p=0.11), and there continued to be a gradual reduction in hsTnI (proportion change 0.79 [95%0.65, 0.95], p=0.012). When comparing patients who continued with aficamten treatment, there were no hemodynamic or biomarker differences were seen whether disopyramide was

withdrawn or continued, although there was a trend to worsening symptoms with prolonged disopyramide use (Diso+Afi Continuous) (Δ LSM [±SE] KCCQ-CSS = -10.2 ±5.0, p=0.052; and NYHA class worsening ≥ 1 = 14.8% [95% CI 0.5, 29.1, p=0.04]) when compared to those patients who discontinued the disopyramide (**Tables 3-4 and Central Illustration Panels A-E**).

A subset from all patients (n=15) with persistent obstruction despite receiving higher baseline doses (≥ 500 mg/day) of disopyramide was analyzed and demonstrated a similar peak hemodynamic response compared to the overall group (mean Δ Valsalva LVOT gradient = -38 mmHg ±51).

Safety

There were no safety events of interest that were directly related to the addition of aficamten, withdrawal of disopyramide, or the concurrent use of aficamten and disopyramide. Furthermore, in the setting of triple-negative inotrope therapy, there were no episodes of LVEF<50% with congestive heart failure. Occurrences of asymptomatic LVEF <50%, new-onset atrial fibrillation, and recurrent atrial fibrillation were infrequent. Safety events of interest are shown in **Table 4**.

DISCUSSION

Over the last several decades, numerous observational studies evaluating the efficacy and safety of disopyramide in patients with oHCM have been published(2-6). These data demonstrate that disopyramide is associated with relief of LVOT obstruction and limiting symptoms in an important subset of oHCM patients, including some patients who enjoy these benefits long-term.(4) Disopyramide treatment is generally safe without substantial risk of proarrythmia or systolic dysfunction. Based on this experience, expert consensus treatment guidelines for HCM have recommended disopyramide, or CMI therapy, as additional medical therapy in patients who

remain symptomatically limited following first line therapy with atrioventricular nodal blocking agents. However, it is currently unknown whether aficamten is safe and effective as combination therapy for patients treated with disopyramide, and what the clinical impacts of various treatment strategies involving these medications may be. Therefore, we leveraged the unique dataset from the aficamten clinical development program to help characterize the impact of aficamten on those HCM patients who have tolerated disopyramide but remained symptomatic due to residual significant LVOT obstruction. Although this study is neither randomized nor a head-to-head comparison of aficamten and disopyramide, herein we provide detailed multimodality evidence to address the important clinical question of how these medications might be used in the clinical environment.

In this study of patients with oHCM with persistent limiting symptoms and outflow tract obstruction despite the use of disopyramide (albeit at modest mean dose) and atrioventricular nodal blocking agents we have shown: (1) the addition of aficamten to this background therapy was safe, well tolerated and resulted in substantial decrease in outflow gradients and improvement in limiting symptoms; (2) Withdrawal of aficamten while maintaining the background therapy resulted in return of LVOT obstruction and worsening symptoms; (3) Withdrawal of disopyramide while maintaining aficamten treatment did not adversely affect LVOT gradients, symptoms, or cardiac biomarkers and was also safe; and (4) Continuation of disopyramide did not confer added treatment advantage over withdrawal.

Aficamten is a CMI that directly targets the sarcomere to normalize myocardial contractility by shifting a proportion of the cardiac myosin to the super-relaxed state, reducing actin-myosin interactions and the pathologic hypercontractility of the HCM myocardium(14). Aficamten has been shown to be safe and effective in improving exercise capacity, symptoms,

hemodynamics and cardiac biomarkers in SEQUOIA-HCM(7). The trial allowed disopyramide as part of individually optimized HCM-specific background medical therapy, and a prior phase II trial, REDWOOD-HCM Cohort 3, evaluated open label aficamten on the background of disopyramide(15). In the absence of a head-to-head trial of aficamten (or any CMI) versus disopyramide, the current analysis leverages data from 3 clinical trials, including a randomized, placebo-controlled clinical trial, to provide the most comprehensive assessment of aficamten versus disopyramide safety and efficacy. These are important data, especially give the guidelines provide similar recommendations for the use of CMIs and disopyramide, and the tendency for physicians to add, rather than replace, therapies for LVOT obstruction.

The current analysis underscores the impact of the disease specific mechanism of action of aficamten. Although the focus in oHCM has traditionally been LVOT gradients and symptoms, NT-proBNP provides a holistic marker of the degree of myocardial wall stress and the myopathic process seen in HCM(16). NT-proBNP is also a highly objective marker that is not susceptible to placebo effect or other confounding factors. In the current analysis, NT-proBNP levels remained elevated in patients receiving disopyramide alone, whereas they were reduced in patients receiving aficamten as monotherapy or in combination with disopyramide. Since nearly all the clinically relevant outcome measures obtained from patients who were withdrawn from disopyramide remained stable, but improved with aficamten monotherapy, these data support the emerging treatment principle that disopyramide may not provide additional clinical benefit in patients who are concurrently treated with aficamten. However, given the relatively small sample size, additional studies should be considered to confirm these initial observations.

Limitations.

This study is subject to the usual biases experienced in open-label studies, however patients were followed prospectively and orthogonal data (symptoms, biomarkers, and echocardiography) appeared to be internally consistent. In the context of an open-label study, subjective measures of functional capacity measures should be interpreted with caution. Additionally, for reference, we were able to include a cohort of patients that were treated with placebo. We included patients who had persistent symptoms and LVOT obstruction despite disopyramide and BB/CCB (medically refractory). Consequently these results cannot be extrapolated to patients who achieve long-term clinical improvement in response to background medical therapy with disopyramide.(4) Although these analyses stem from three well-conducted prospective clinical trials, they are post-hoc, without randomization, and the results were not adjusted for multiple testing.

Unlike consensus guidelines developed for the treatment of heart failure with reduced LVEF, and due to the lack of controlled trials evaluating standard of care medical therapies in HCM, the societal guidelines for HCM lack specific target doses for BB, CCB or disopyramide. As such, investigators were instructed to ensure patients were receiving maximally tolerated background medical therapy according to these guidelines. Previously the mean daily dose of 501± 30 mg appeared to be effective and well tolerated in a study of 221 patients for over 5 years(5), complemented by dose-response relationship data on disopyramide that has been shown in-vitro(17), in the echocardiographic laboratory (18), and in the catheterization laboratory (19). But this metric, the mean dose of disopyramide observed in our study (331 mg ±146) was modest. However, while limited by a small sample size, the subset of patients with persistent obstruction in this analysis receiving ≥ 500 mg disopyramide per day did demonstrate a similar hemodynamic response to the overall group (mean Δ Valsalva LVOT gradient = -38 mmHg

±51)., with doses <400 mg/day yielding low plasma drug concentrations (17-19).

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Conclusions

In the subgroup of patients with oHCM who remain limited with residual outflow gradients despite use of disopyramide at modest dose ranges, combination therapy with aficamten and disopyramide was safe and well tolerated, but did not enhance clinical efficacy compared to aficamten alone. Indeed, withdrawal of disopyramide in these patients did not compromise the clinical efficacy of aficamten or result in increased atrial fibrillation. These data suggest there may be limited value for continuation of disopyramide therapy in patients receiving aficamten.

Clinical Perspectives

Competency in Medical Knowledge: Patients with obstructive hypertrophic cardiomyopathy who remain obstructed on disopyramide therapy had significant relief of their left ventricular outflow tract obstruction and improved symptoms and biomarkers with the addition of aficamten, while the withdrawal of disopyramide did not compromise efficacy of aficamten.

Translational Outlook: Disopyramide and aficamten have distinct mechanisms of action and their combined use is safe.

References

1. Ommen SR, Ho CY, Asif IM et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2024.
2. Adler A, Fourey D, Weissler-Snir A, Hindieh W, Chan RH, Gollob MH, Rakowski H. Safety of Outpatient Initiation of Disopyramide for Obstructive Hypertrophic Cardiomyopathy Patients. J Am Heart Assoc 2017;6.
3. Sherrid MV, Barac I, McKenna WJ et al. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;45:1251-8.
4. Massera D, Sherrid MV, Adlestein E et al. Disopyramide Revisited for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy: Efficacy and Safety in Patients Treated for at Least 5 Years. J Am Heart Assoc 2025;14:e037639.
5. Sherrid MV, Shetty A, Winson G et al. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with β-blockade or verapamil. Circ Heart Fail 2013;6:694-702.
6. Ball W, Ivanov J, Rakowski H et al. Long-term survival in patients with resting obstructive hypertrophic cardiomyopathy comparison of conservative versus invasive treatment. J Am Coll Cardiol 2011;58:2313-21.
7. Maron MS, Masri A, Nassif ME et al. Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy. N Engl J Med 2024;390:1849-1861.
8. Owens AT, Masri A, Abraham TP et al. Aficamten for Drug-Refractory Severe

Obstructive Hypertrophic Cardiomyopathy in Patients Receiving Disopyramide: REDWOOD-HCM Cohort 3. J Card Fail 2023.

9. Olivotto I, Oreziak A, Barriales-Villa R et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet 2020;396:759-769.
10. Desai MY, Owens A, Geske JB et al. Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy. J Am Coll Cardiol 2022;80:95-108.
11. Garcia-Pavía PB, O.; Burroughs, M. et al. Aficamten vs Metoprolol for Obstructive Hypertrophic Cardiomyopathy: MAPLE-HCM Rationale, Study Design, and Baseline Characteristics. Journal of the American College of Cardiology: Heart Failure 2025;13:346-357.
12. Owens AT, Masri A, Abraham TP et al. Efficacy and safety of aficamten and disopyramide coadministration in obstructive hypertrophic cardiomyopathy: results from REDWOOD-HCM cohort 3. Journal of the American College of Cardiology 2022;79:244-244.
13. Masri A, Choudhury L, Barriales-Villa R et al. Standard-of-Care Medication Withdrawal in Patients With Obstructive Hypertrophic Cardiomyopathy Receiving Aficamten in FOREST-HCM. J Am Coll Cardiol 2024;84:1839-1849.
14. Haraf R, Habib H, Masri A. The Revolution of Cardiac Myosin Inhibitors in Patients With Hypertrophic Cardiomyopathy. Can J Cardiol 2024;40:800-819.
15. Owens AT, Masri A, Abraham TP et al. Aficamten for Drug-Refractory Severe Obstructive Hypertrophic Cardiomyopathy in Patients Receiving Disopyramide:

REDWOOD-HCM Cohort 3. J Card Fail 2023;29:1576-1582.

16. Geske JB, McKie PM, Ommen SR, Sorajja P. B-type natriuretic peptide and survival in hypertrophic cardiomyopathy. J Am Coll Cardiol 2013;61:2456-2460.

17. Coppini R, Ferrantini C, Pioner JM et al. Electrophysiological and Contractile Effects of Disopyramide in Patients With Obstructive Hypertrophic Cardiomyopathy: A Translational Study. JACC Basic Transl Sci 2019;4:795-813.

18. Sherrid M, Delia E, Dwyer E. Oral disopyramide therapy for obstructive hypertrophic cardiomyopathy. Am J Cardiol 1988;62:1085-8.

19. Kimball BP, Bui S, Wigle ED. Acute dose-response effects of intravenous disopyramide in hypertrophic obstructive cardiomyopathy. Am Heart J 1993;125:1691-7.

Figure Legends

Figure 1. Study schema and patient disposition

[a]Excluding patients enrolled in China (n=46) who did not roll over into FOREST-HCM

Assessments at each time point: Clinical, NYHA class, KCCQ-CSS, LVEF, LVOT gradients, NTproBNP, HsTnI, adverse events.

Diso-Afi Withdrawal, concomitant disopyramide and aficamten therapy followed by withdrawal of aficamten; Diso-Pbo, concomitant disopyramide and placebo therapy; Afi-Diso Withdrawal, concomitant aficamten and disopyramide therapy followed by withdrawal of disopyramide; Diso+Afi Continuous, concomitant aficamten and disopyramide therapy throughout study; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; HsTnI, high-sensitivity troponin I; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Central Illustration: Measures of disopyramide and aficamten efficacy.

Data are geometric mean (CV%)

[a]Diso+Afi Continuous group did not have washout and was assessed again during the next follow up visit.

Diso-Afi Withdrawal, concomitant disopyramide and aficamten therapy followed by withdrawal of aficamten; Diso-Pbo, concomitant disopyramide and placebo therapy; Afi-Diso Withdrawal, concomitant aficamten and disopyramide therapy followed by withdrawal of disopyramide; Diso+Afi Continuous, concomitant aficamten and disopyramide therapy throughout study; CV, coefficient of variation; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract;

NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

Table 1: Baseline characteristics of the 4 groups.

Variables	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
Age (years), mean (SD)	58.0 (13.3)	62.8 (10.4)	60.9 (15.0)	63.0 (10.9)
Female sex, n (%)	15 (51.7)	7 (35.0)	9 (52.9)	14 (51.9)
Race, n (%)				
White	24 (82.8)	19 (95.0)	16 (94.1)	23 (85.2)
Black or African American	3 (10.3)	0	0	2 (7.4)
Asian	2 (6.9)	1 (5.0)	1 (5.9)	2 (7.4)
BMI (kg/m^2), mean (SD)	29.7 (4.7)	29.6 (3.8)	29.6 (4.4)	28.7 (3.5)
Known HCM-causing gene mutation or positive family history	12 (41.4)	4 (20.0)	6 (35.3)	9 (33.3)
Beta-blockers, n (%)	26 (89.7)	19 (95.0)	14 (82.4)	25 (92.6)
Calcium channel blockers (verapamil or diltiazem), n (%)	4 (13.8)	1 (5.0)	3 (17.6)	3 (11.1)
Disopyramide, n (%)	29 (100)	20 (100)	17 (100)	27 (100)
Mean daily disopyramide dose, mg (SD)	352.6 (146.74)	302.5 (93.86)	276.5 (128.84)	364.3 (175.82)
≥2 background HCM medications	29 (100)	19 (95.0)	17 (100)	26 (96.3)
Baseline NYHA class, n (%)				
I	0	0	1 (5.9)	1 (3.7)

Variables	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
II	19 (65.5)	13 (65.0)	8 (47.1)	16 (59.3)
III	10 (34.5)	6 (30.0)	8 (47.1)	10 (37.0)
IV	0	1 (5.0)	0	0
KCCQ-CSS, mean (SD)	71 (17)	71 (22)	59 (21)	69 (21)
LVEF (%), mean (SD)	69 (6)	69 (9)	68 (5)	69 (7)
Resting LVOT gradient (mmHg), mean (SD)	51 (24)	64 (30)	60 (33)	54 (37)
Valsalva LVOT gradient (mmHg), mean (SD)	90 (37)	94 (43)	91 (41)	87 (34)
NT-proBNP (pg/mL), median (Q1, Q3); GeoMean (Geo CV%)	1231.0 (372.0, 1689.0); 839.1 (172.8)	1081.5 (605.5, 1925.0); 1005.3 (112.4)	1129.0 (1051.0, 1643.0); 980.0 (93.8)	1139.0 (508.0, 1619.0); 912.3 (140.2)
HsTnI (ng/L), GeoMean (Geo CV%)	11.6 (82.1)	12.8 (137.1)	11.2 (102.4)	10.2 (63.1)
ECG QRS duration (ms), mean (SD)	109.1 (20.3)	130.8 (35.7)	124.9 (26.9)	113.8 (27.7)
ECG QTcB interval (ms), mean (SD)	468.5 (27.4)	484.1 (33.0)	483.3 (31.3)	474.9 (35.4)
ECG QTcF interval (ms), mean (SD)	467.7 (27.2)	487.5 (32.9)	483.6 (32.4)	471.6 (34.8)

Afi-Diso Withdrawal, concomitant aficamten and disopyramide therapy followed by withdrawal of disopyramide; BMI, body mass index; CV, coefficient of variation; Diso+Afi Continuous, concomitant aficamten and disopyramide therapy throughout study; Diso-Afi Withdrawal, concomitant disopyramide and aficamten therapy followed by withdrawal of aficamten; Diso-Pbo, concomitant disopyramide and placebo therapy; ECG, electrocardiogram; GeoMean, geometric mean; HCM, hypertrophic cardiomyopathy; hsTnI, high-sensitivity troponin I; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QTcB, Bazett corrected QT interval; QTcF, Fridericia corrected QT interval; SD, standard deviation;

Table 2. Treatment effect on Echocardiographic Endpoints across Groups.

Endpoint, Timepoint	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
Resting LVOT gradient (mmHg)				
Baseline, mean ±SD	50.1 ±24.1	64.1 ±29.7	58.0 ±32.2	54.1 ±37.2
Add-on therapy	17.3 ±17.6	62.5 ±26.8	18.8 ±14.0	20.7 ±19.2
LS mean change ±SE (p-value)	–27.0 ±3.6 (<0.0001)	14.6 ±4.3 (<0.001)	–27.5 ±4.7 (<0.0001)	–24.6 ±3.6 (<0.0001)
LS mean difference vs. Diso-Afi Withdrawal ±SE (p-value)	–	–	–0.5 ±5.8 (0.93)	2.4 ±5.0 (0.64)
LS mean difference vs. Diso-Pbo ±SE (p-value)	–41.5 ±5.5 (<0.0001)	–	–42.1 ±6.2 (<0.0001)	–39.2 ±5.5 (<0.0001)
LS mean difference vs. Afi-Diso Withdrawal ±SE (p-value)	–	–	–	2.9 ±5.8 (0.62)
Withdrawal (except Diso+Afi)	51.9 ±37.1	62.5 ±25.5	12.9 ±8.4	20.0 ±23.8
LS mean change ±SE (p-value)	44.1 ±7.4 (<0.0001)	–7.7 ±7.9 (0.34)	3.0 ±8.9 (0.74)	7.5 ±7.1 (0.30)

Endpoint, Timepoint	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
LS mean difference vs. Diso-Afi Withdrawal ±SE (p-value)	–	–	-41.1 ±10.3 (0.001)	–36.6 ±8.9 (<0.001)
LS mean difference vs. Diso-Pbo ±SE (p-value)	51.9 ±11.9 (<0.001)	–	10.8 ±12.8 (0.41)	15.3 ±11.6 (0.20)
LS mean difference vs. Afi-Diso Withdrawal ±SE (p-value)	–	–	–	4.5 ±10.3 (0.67)
Valsalva LVOT gradient (mmHg)				
Baseline, mean ±SD	90.3 ±38.5	93.8 ±42.8	86.6 ±37.3	87.2 ±34.4
Add-on therapy	34.6 ±26.2	98.1 ±27.2	37.4 ±24.3	39.7 ±25.8
LS mean change ±SE (p-value)	–39.2 ±5.0 (<0.0001)	23.8 ±5.8 (<0.001)	–35.7 ±6.4 (<0.0001)	–33.5 ±4.9 (<0.0001)
LS mean difference vs. Diso-Afi Withdrawal ±SE (p-value)	–	–	3.48 ±8.0 (0.66)	5.7 ±6.9 (0.41)
LS mean difference vs. Diso-Pbo ±SE (p-value)	–62.9 ±7.5 (<0.0001)	–	–59.5 ±8.5 (<0.0001)	–57.3 ±7.5 (<0.0001)

Endpoint, Timepoint	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
LS mean difference vs. Afi-Diso Withdrawal ±SE (p-value)	–	–	–	2.2 ±8.0 (0.79)
Withdrawal (except Diso+Afi)	78.7 ±37.9	83.3 ±25.3	25.9 ±27.1	34.4 ±26.5
LS mean change ±SE (p-value)	65.5 ±9.4 (<0.0001)	–31.6 ±10.0 (0.02)	8.2 ±11.2 (0.49)	13.0 ±9.0 (0.19)
LS mean difference vs. Diso-Afi Withdrawal ±SE (p-value)	–	–	–57.4 ±12.8 (0.004)	–52.5 ±11.1 (0.003)
LS mean difference vs. Diso-Pbo ±SE (p-value)	97.1 ±15.1 (<0.0001)	–	39.8 ±16.2 (0.04)	44.6 ±14.7 (0.01)
LS mean difference vs. Afi-Diso Withdrawal ±SE (p-value)	–	–	–	4.8 ±12.8 (0.72)
LVEF (%)				
Baseline, mean ±SD	69.7 ±6.8	69.4 ±8.9	67.7 ±4.6	68.6 ±7.1
Add-on therapy	66.4 ±6.9	69.6 ±5.3	63.7 ±5.0	66.1 ±5.4
LS mean change ±SE (p-value)	–2.0 ±1.0 (0.052)	1.2 ±1.2 (0.30)	–4.0 ±1.3 (0.003)	–1.9 ±1.0 (0.06)

Endpoint, Timepoint	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
LS mean difference vs. Diso-Afi Withdrawal ±SE (p-value)	–	–	–2.0 ±1.7 (0.24)	0.14 ±1.4 (0.92)
LS mean difference vs. Diso-Pbo ±SE (p-value)	–3.3 ±1.6 (0.04)	–	–5.3 ±1.8 (0.004)	–3.1 ±1.5 (0.046)
LS mean difference vs. Afi-Diso Withdrawal ±SE (p-value)	–	–	–	2.1 ±1.7 (0.20)
Withdrawal (except Diso+Afi)	69.4 ±7.4	70.0 ±8.3	61.0 ±5.7	66.7 ±6.0
LS mean change ±SE (p-value)	2.8 ±1.4 (0.052)	0.7 ±1.6 (0.65)	–3.4 ±1.9 (0.07)	0.3 ±1.4 (0.85)
LS mean difference vs. Diso-Afi ±SE (p-value)	–	–	–6.3 ±2.3 (0.009)	–2.6 ±2.0 (0.20)
LS mean difference vs. Diso-Pbo ±SE (p-value)	2.1 ±2.2 (0.34)	–	–4.2 ±2.5 (0.10)	–0.5 ±2.1 (0.83)
LS mean difference vs. Afi-Diso ±SE (p-value)	–	–	–	3.7 ±2.3 (0.11)

Afi-Diso Withdrawal, concomitant aficamten and disopyramide therapy followed by withdrawal of disopyramide; Diso+Afi Continuous, concomitant aficamten and disopyramide therapy throughout study; Diso-Afi Withdrawal, concomitant disopyramide and aficamten therapy followed by withdrawal of aficamten; Diso-Pbo, concomitant disopyramide and placebo therapy; LS, least squares; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; SD, standard deviation; SE, standard error.

Table 3. Treatment effect on clinical endpoints across groups.

Endpoint, Timepoint	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
NYHA class improvement by ≥1 class (%)				
Baseline	–	–	–	–
Add-on therapy, % (95% CI), p-value	77.8 (61.0, 94.5), <0.0001	30.0 (8.0, 52.0), 0.01	81.3 (59.8, 100), <0.0001	74.1 (56.4, 91.7), <0.0001
Common rate difference vs. Diso-Afi Withdrawal (95% CI), p-value	–	–	3.5 (-23.0, 30.0), 0.79	–3.7 (-27.5, 20.1), 0.76
Common rate difference vs. Diso-Pbo (95% CI), p-value	47.8 (21.4, 74.2), <0.001	–	51.3 (21.1, 81.4), 0.001	44.1 (16.9, 71.2), 0.002
Common rate difference vs. Afi-Diso Withdrawal (95% CI), p-value	–	–	–	–7.2 (–34.6, 20.3), 0.60
Withdrawal (except Diso+Afi), % (95% CI), p-value	0.0 (0.0, 0.0), >0.999	0.0 (0.0, 0.0), >0.999	18.8 (–2.7, 40.2), 0.08	25.9 (8.3, 43.6), 0.006

Endpoint, Timepoint	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
Common rate difference vs. Afi-Diso (95% CI), p-value	–	–	–	7.2 (–20.3, 34.6), 0.60
NYHA class worsening by ≥1 class (%)				
Add-on therapy, % (95% CI), p-value	0.0 (0.0, 0.0), >0.999	0.0 (0.0, 0.0), >0.999	0.0 (0.0, 0.0), >0.999	0.0 (0.0, 0.0) >0.999
Withdrawal (except Diso+Afi), % (95% CI), p-value	70.4 (52.0, 88.8), <0.0001	10.0 (–4.4, 24.4), 0.16	0.0 (0.0, 0.0), >0.999	14.8 (0.5, 29.1), 0.04
KCCQ-CSS				
Baseline, mean ± SD	72.0 ±16.9	70.5 ±22.0	60.2 ±21.4	68.5 ±21.4
Add-on therapy	86.4 ±12.7	75.4 ±19.3	79.7 ±17.2	88.7 ±11.5
LS mean change ±SE (p-value)	12.3 ±3.3 (<0.001)	2.0 ±2.9 (0.49)	10.4 ±3.3 (0.003)	16.1 ±2.5 (<0.0001)
LS mean difference vs. Diso-Afi Withdrawal ±SE (p-value)	–	–	–1.9 ±4.7 (0.68)	3.7 ±4.1 (0.37)
LS mean difference vs. Diso-Pbo ±SE (p-value)	10.3 ±4.4 (0.02)	–	8.4 ±4.3 (0.06)	14.1 ±3.8 (<0.001)

Endpoint, Timepoint	Diso-Afi Withdrawal (N=29)	Diso-Pbo (N=20)	Afi-Diso Withdrawal (N=17)	Diso+Afi Continuous (N=27)
LS mean difference vs. Afi-Diso Withdrawal ±SE (p-value)	–	–	–	5.7 ±4.1 (0.17)
Withdrawal (except Diso+Afi)	66.4 ±22.8	75.1 ±18.2	82.9 ±18.1	85.3 ±19.4
LS mean change ±SE (p-value)	–24.3 ±4.2 (<0.0001)	–0.4 ±3.5 (0.92)	1.5 ±3.9 (0.70)	–8.7 ±3.3 (0.01)
LS mean difference vs. Diso-Afi Withdrawal ±SE (p-value)	–	–	25.9 ±5.7 (<0.0001)	15.7 ±5.1 (0.004)
LS mean difference vs. Diso-Pbo ±SE (p-value)	–24.0 ±5.5 (<0.001)	–	1.9 ±5.3 (0.72)	–8.3 ±4.8 (0.1)
LS mean difference vs. Afi-Diso Withdrawal ±SE (p-value)	–	–	—	—10.2 ±5.0 (0.052)

Afi-Diso Withdrawal, concomitant aficamten and disopyramide therapy followed by withdrawal of disopyramide; CI, confidence interval; Diso+Afi Continuous, concomitant aficamten and disopyramide therapy throughout study; Diso-Afi Withdrawal, concomitant disopyramide and aficamten therapy followed by withdrawal of aficamten; Diso-Pbo, concomitant disopyramide

and placebo therapy; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LS, least squares; NYHA, New York Heart Association; SD, standard deviation; SE, standard error.

Table 4. Safety outcomes of interest in the study population

	Diso-Afi Withdrawal **(N=29)** **n (%), m**	**Diso-Pbo (N=20)** **n (%), m**	**Afi-Diso** Withdrawal **(N=17)** **n (%), m**	**Diso+Afi Continuous (N=27)** **n (%), m**
Patients died during the study	0	0	0	0
LVEF < 50%	3 (10.3), 3	0	1 (5.9), 1	1 (3.7), 2
Atrial fibrillation or flutter	2 (6.9), 2	1 (5.0), 1	1 (5.9), 1	2 (7.4), 2
New onset	0	0	1 (5.9), 1	1 (3.7), 1
Recurrent	2 (6.9), 2	1 (5.0), 1	0	1 (3.7), 1
LVEF < 50% with Heart Failure	0	0	0	0

n=count of patients with events; m=count of events

Afi-Diso Withdrawal, concomitant aficamten and disopyramide therapy followed by withdrawal of disopyramide; Diso+Afi Continuous, concomitant aficamten and disopyramide therapy throughout study; Diso-Afi Withdrawal, concomitant disopyramide and aficamten combination therapy followed by withdrawal of aficamten; Diso-Pbo, concomitant disopyramide and placebo therapy; LVEF, left ventricular ejection fraction.