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ORIGINAL RESEARCH

CARDIOMYOPATHIES

Aficamten Treatment for Symptomatic Obstructive Hypertrophic Cardiomyopathy

48-Week Results From FOREST-HCM

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ABSTRACT

BACKGROUND Long-term safety and efficacy data for aficamten in symptomatic obstructive hypertrophic cardiomyopathy are needed.

OBJECTIVES This study aims to evaluate 48-week experience from the ongoing FOREST-HCM (A Follow-Up, Open-Label, Research Evaluation of Sustained Treatment With Aficamten [CK-3773274] in Hypertrophic Cardiomyopathy) study.

METHODS Obstructive hypertrophic cardiomyopathy participants in an aficamten study (REDWOOD-HCM [Dose-finding Study to Evaluate the Safety, Tolerability, PK, and PD of CK-3773274 in Adults With HCM; NCT04219826]; SEQUOIA-HCM [Aficamten vs Placebo in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; NCT05186818]) could enroll in this phase 2/3, open-label, extension study. Participants received aficamten 5 mg once daily titrated ≤20 mg based on site-read echocardiographic assessments of Valsalva left ventricular outflow tract gradient and left ventricular ejection fraction.

RESULTS From May 2021 to October 2023, 213 participants enrolled; 46 participants with 48 weeks of follow-up were evaluated (mean age: 59.7 years; female: n = 26 [56.5%]). There were rapid, substantial, and sustained reductions in mean resting (−40 ± 34 mm Hg) and Valsalva peak left ventricular outflow tract gradient (−53 ± 39 mm Hg) from baseline to week 48. A total of 82% experienced ≥1 NYHA functional class improvement; 31% experienced a 20-point improvement in Kansas City Cardiomyopathy Questionnaire-Clinical Summary score. There were substantial reductions (mean change) in maximum left ventricular wall thickness (−1.2 ± 1.6 mm; $P < 0.0001$), left atrial volume index (−3.5 ± 6.6 mL/m^2; $P = 0.0008$), lateral E/e′ (−2.2 ± 6.1; $P = 0.02$), and cardiac biomarkers ($P \leq 0.0031$). Aficamten was well tolerated with 2 (4.3%) asymptomatic and transient instances of left ventricular ejection fraction <50% (range: 47%-49%), neither resulting in drug discontinuation, and no new-onset atrial fibrillation.

CONCLUSIONS Aficamten treatment over 48 weeks was well tolerated and associated with substantial and durable relief of obstruction and symptom burden, lower cardiac biomarker levels, and cardiac phenotypic changes, which may indicate favorable cardiac remodeling. (A Follow-Up, Open-Label, Research Evaluation of Sustained Treatment With Aficamten [CK-3773274] in Hypertrophic Cardiomyopathy [FOREST-HCM]; NCT04848506)
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ABBREVIATIONS AND ACRONYMS

CMI = cardiac myosin inhibitor

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 = left ventricular outflow tract

NT-proBNP = N-terminal pro-B-type natriuretic peptide

oHCM = obstructive hypertrophic cardiomyopathy

pVO_2 = peak oxygen uptake

SRT = septal reduction therapy

TEAE = treatment-emergent adverse event

Historical guideline-recommended therapies for symptomatic obstructive hypertrophic cardiomyopathy (oHCM) did not address the hypercontractility underlying the development of left ventricular outflow tract (LVOT) obstruction, frequently associated with symptoms of exertional angina, dyspnea, and lightheadedness.[1,2] In the most recently updated European Society of Cardiology guidelines[3] and ACC (American College of Cardiology)/AHA (American Heart Association) guidelines,[4] the cardiac myosin adenosine triphosphatase inhibitor mavacamten was recommended (Class 1) as a second-line agent for management of symptomatic oHCM in adults. Aficamten (formerly CK-3773274), a next-in-class cardiac myosin inhibitor (CMI), reduces the number of active actin-myosin cross bridges within the sarcomere. Its differentiating features with respect to mavacamten include a shallower dose-response relationship with the intent of minimizing reductions in left ventricular ejection fraction (LVEF) with dose increases, a shorter half-life enabling more rapid dose escalation, and no substantial cytochrome P450 induction or inhibition.[5-7] In the short term, aficamten has demonstrated both safety and effectiveness in reducing resting and provocable LVOT gradients in patients with oHCM. Moreover, it has been associated with improvements in exercise capacity, symptom burden, and overall health status, along with favorable changes in biomarkers of wall stress and myocardial injury.[8,9] Longer-term studies of mavacamten have reported low LVEF events throughout the treatment period,[10-13] supporting the critical need for evaluating CMIs over longer treatment periods. Here, we report on the safety and efficacy of aficamten in patients with oHCM over 48 weeks in the FOREST-HCM (A Follow-Up, Open-Label, Research Evaluation of Sustained Treatment With Aficamten [CK-3773274] in Hypertrophic Cardiomyopathy; NCT04848506) study.

METHODS

STUDY DESIGN. The phase 2/3 FOREST-HCM is an ongoing open-label extension study running for approximately 5 years for eligible patients with oHCM and nonobstructive hypertrophic cardiomyopathy (HCM) who participated in parent clinical trials of aficamten (REDWOOD-HCM [Dose-finding Study to Evaluate the Safety, Tolerability, PK, and PD of CK-3773274 in Adults With HCM] and SEQUOIA-HCM [Aficamten vs Placebo in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy]).[8,9,14,15] The aim of FOREST-HCM is to assess the safety and tolerability of long-term treatment with aficamten, and long-term treatment effects on cardiac function, symptom burden, and health status. The protocol was approved by site-specific institutional review boards and funded by Cytokinetics. Employees of Cytokinetics and the academic investigators participate in data analysis and vouch for the accuracy of the data. All participants provided 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.

STUDY POPULATION. Eligible participants include adults ≥18 years of age who completed a parent study and have LVEF ≥55% at study entry. Patients with oHCM are adjudicated to have significant obstruction based on baseline assessments during participation in

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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the parent study. Main exclusion criteria include prior history of LVEF <45% or stress cardiomyopathy at any time during their clinical course, and any confirmed LVEF <40% with an associated dose interruption during participation in a prior study with aficamten. A full list of the inclusion and exclusion criteria and study schema is provided in Supplemental Table 1 and Supplemental Figure 1.

INTERVENTION. Aficamten was started at 5 mg orally once daily in all participants, with dose up-titrations by 5 mg at week 2, 4, and 6 visits, to a maximum 15 mg until December 2021 when protocol amendment 3 was released and allowed an increase to 20 mg once daily if site-read echocardiography criteria were met (LVEF ≥55% and Valsalva LVOT gradient ≥30 mm Hg). If the highest dose of aficamten was not achieved during the initial 6-week titration period, the dose could be up-titrated by 5 mg at any subsequent visit provided these echocardiographic criteria were met. Participants who did not meet these criteria were maintained at their current dose. Investigators also integrated their clinical judgment with echocardiographic data when deciding whether to up-titrate dose (dose up-titration was not compulsory based solely on echocardiographic parameters). Participants experiencing LVEF ≥40% to <50% at any visit were returned to the next lower dose. An assessment of LVEF was required approximately 2 weeks after any dose titration. Aficamten dosing was permanently discontinued if LVEF was <50% before or at the week 2 visit and was temporarily interrupted for LVEF <40% at any other visit with the opportunity to restart after discussion with the medical monitor after the LVEF was ≥55%.

ENDPOINTS. The study endpoints are listed in Supplemental Table 2. The primary endpoint of this ongoing study is to determine the safety and tolerability of aficamten in symptomatic oHCM patients, assessed by the incidence of reported treatment-emergent adverse events (TEAEs), serious adverse events, and LVEF <50%. Secondary endpoints include long-term effects of aficamten on hemodynamic response (resting and Valsalva LVOT gradients). Key exploratory endpoints include assessments of the long-term effects of aficamten on cardiac biomarkers, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI), on echocardiographic measurements of cardiac structure and function, and on functional outcomes and symptoms (NYHA functional class and Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score [KCCQ-CSS]). The KCCQ-CSS combines the total symptom, physical, and social limitation scales to provide an inclusive summary of patients' symptom burden and functional status. Scores for each domain range from 0 to 100, with 0 representing the worst symptoms and function, and 100 representing low symptom burden and high functional status. Scores of 0 to 24 represent very poor to poor, 25 to 49 represent poor to fair, 50 to 74 represent fair to good, and 75 to 100 represent good to excellent symptom burden and functional status. A ≥5-point increase in KCCQ-CSS is the clinically meaningful threshold for patients with oHCM.[16-18]

STATISTICAL ANALYSIS. Due to the exploratory and open-label nature of the study, no formal sample size calculation was performed. Safety analyses were performed based on the safety analysis set consisting of participants who received ≥1 dose of aficamten and have been followed for at least 48 weeks (N = 46). For safety analyses, statistics were descriptive, and no hypothesis testing was planned or conducted. The efficacy analyses were performed based on the modified efficacy analysis set consisting of participants who received ≥1 dose of study drug, had ≥1 postbaseline efficacy assessment during the study (excluding 2 participants from 1 site due to a Good Clinical Practice violation), and had been followed for ≥48 weeks (n = 45). In the efficacy analyses, descriptive statistics for each parameter and change from baseline (including 95% CI) are provided by time point for the number of participants who had reached that time point by data cutoff (October 31, 2023). Baseline characteristics were summarized using mean ± SD or median (Q1-Q3) for continuous variables, and counts and percentages for categorical variables. Because dose titration was based on site-read echocardiography criteria, we describe Valsalva and resting LVOT gradients and LVEF as reported by sites, whereas all other echocardiographic parameters of diastolic function and structural changes are reported based on core-laboratory interpretation.

RESULTS

BASELINE CHARACTERISTICS. Between May 28, 2021, and October 31, 2023, 213 adults with oHCM enrolled in FOREST-HCM: 45 were from REDWOOD-HCM (21%) and 168 were from SEQUOIA-HCM (79%). By October 31, 2023, 46 (11%) had completed 48 weeks of follow-up and were included in this analysis (86.6 patient-years of exposure). The mean age was 59.7 ± 12.8 years, and 26 (56.5%) were female. Symptom burden was substantial, with a mean KCCQ-CSS score of 73 ± 18, and 22 participants (47.8%) had NYHA functional class III. Background therapy

included 36 participants (78.3%) on beta-blockers, 8 (17.4%) on nondihydropyridine calcium channel blockers (verapamil or diltiazem), and 9 (19.6%) on disopyramide. Three participants (6.5%) were not receiving any background therapy. Echocardiographic parameters were consistent with oHCM with a maximal wall thickness of 19.6 ± 3.1 mm, severe obstruction (resting and Valsalva LVOT gradients of 52 ± 33 mm Hg and 81 ± 35 mm Hg, respectively), and mean LVEF of 69% ± 5%. Participants showed evidence of diastolic dysfunction, with elevated left atrial volume index of 36.0 ± 8.0 mL/m^2, elevated lateral E/e′ of 15.4 ± 7.6, and septal E/e′ of 18.9 ± 7.7. Participants had increased myocardial wall stress and myocardial injury as evidenced by elevated median NT-proBNP of 733 pg/mL (Q1-Q3: 306-1,874 pg/mL) and hs-cTnI of 11.1 ng/L (Q1-Q3: 4.8-21.3 ng/L), respectively (**Tables 1 and 2**).

TABLE 1 Baseline Demographic and Clinical Characteristics (N = 46)

Age, y	59.7 ± 12.8 (23-82)
Female	26 (56.5)
Race	
White/Black/Asian/other	94/4/2/0
BMI, kg/m^2	29.7 ± 6.1 (22-51)
Comorbidities	
History of atrial fibrillation	6 (13.0)
Syncope	9 (19.6)
Hypertension	16 (34.8)
HCM history	
Positive family history of HCM	8 (17.4)
Time since initial HCM diagnosis, y	4.9 ± 5.3 (1-24)
SRT eligible	19 (41.3)
HCM symptoms	
NYHA functional class	
I-II	24 (52.2)
III	22 (47.8)
KCCQ-CSS	73 ± 18 (35-100)
HCM medical therapy	
Beta-blocker use	36 (78.3)
Calcium channel blocker use	8 (17.4)
Disopyramide use	9 (19.6)
No background therapy	3 (6.5)
Biomarkers	
NT-proBNP, pg/mL	657.5 (306-1,874)
hs-cardiac-TnI, ng/L	11.2 (5-20)
Echocardiography parameters[a]	
LVEF, %	69 ± 5
Rest LVOT gradient, mm Hg	52 ± 33
Valsalva LVOT gradient, mm Hg	82 ± 35
Maximal wall thickness, mm	19.6 ± 3.1
LAVI, mL/m^2	36.0 ± 8.0
Lateral E/e′	15.4 ± 7.6
Septal E/e′	18.9 ± 7.7

Values are mean ± SD (range), mean ± SD, n (%), or median (Q1-Q3), unless otherwise indicated. [a]Core laboratory read.

HCM = hypertrophic cardiomyopathy; hs-cardiac-TnI = high-sensitivity cardiac troponin I; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-pro BNP = N-terminal pro–B-type natriuretic peptide; SRT = septal reduction therapy.

DOSE ACHIEVED. At week 48, the distribution of aficamten doses were as follows: 11.4% at 5 mg, 13.6% at 10 mg, 38.6% at 15 mg, and 36.4% at 20 mg (Supplemental Figure 2).

SAFETY. Aficamten was well tolerated, with TEAEs resulting in drug dose reduction occurring in 2 participants (4.3%) (**Table 3**). One dose reduction occurred in a patient who experienced a reduced LVEF in the setting of alcohol-induced paroxysmal atrial fibrillation (previous paroxysm of atrial fibrillation also associated with LVEF <50% before participation in the clinical trial) with resultant protocol-directed dose reduction from 15 to 10 mg at week 9. This participant experienced symptomatic atrial fibrillation with rapid ventricular response in the week after dose reduction and underwent temporary dose interruption and pharmacologic cardioversion with amiodarone. A second participant underwent dose reduction in the setting of an incorrectly calculated QT interval, whereby it was initially thought to have prolongation. The electrocardiography core laboratory subsequently calculated the QT interval which was not prolonged, and the dose was increased thereafter. There were no instances of new-onset atrial fibrillation, and 2 participants (4.3%) had recurrence of their known paroxysmal atrial fibrillation. Serious adverse events (atrial fibrillation, acute myocardial infarction, embolic stroke, road traffic accident, and cervical fracture) occurred among 4 participants (8.7%), none of which were deemed to be related to aficamten per the investigator. There were no deaths.

Two participants had LVEF <50% (range: 47%-49%), one of which was in the setting of alcohol-induced atrial fibrillation (previously described). The other was asymptomatic and reported on a per-protocol echocardiogram at week 48 visit. The core laboratory reported both of these as LVEF >50%. Because dose titrations were made based off site-read LVEF, both underwent dose reduction with subsequent increase in LVEF, and neither incident was associated with heart failure signs or symptoms. One participant with persistent LVOT obstruction elected to undergo myectomy after week 48.

HEMODYNAMIC CHANGES. By 6 weeks of aficamten treatment, mean resting LVOT gradient declined by 67% from baseline 52 ± 33 mm Hg to 17 ± 14 mm Hg and remained <30 mm Hg through the ensuing

TABLE 2 Changes From Baseline in Echocardiographic Parameters

	Baseline (n = 45)	Week 12 (n = 45)	Week 48 (n = 45)	Change From Baseline to Week 48	*P* Value (Baseline to Week 48)
Maximal wall thickness, mm	19.6 ± 3.1	(No data transferred for week 12) week 24: 19.0 ± 3.2	18.5 ± 3.3	−1.2 ± 1.6	<0.0001
LV mass index, g/m^2	129.4 ± 26.9	122.9 ± 26.7	119.5 ± 30.1	−9.0 ± 25.2	0.0226
LAVI, mL/m^2	36.0 ± 8.0	33.0 ± 9.0	32.4 ± 10.4	−3.5 ± 6.6	0.0008
Septal E/e′	18.9 ± 7.7	16.4 ± 6.9	16.4 ± 6.3	−2.6 ± 5.4	0.0020
Lateral E/e′	15.4 ± 7.6	13.6 ± 7.6	13.4 ± 7.4	−2.2 ± 6.1	0.0225
LVEDV, mL	68.2 ± 19.4	69.5 ± 22.9	68.0 ± 23.1	0.2 ± 12.4	0.9221
LVESV, mL	19.2 ± 8.2	22.6 ± 10.8	23.5 ± 11.2	4.6 ± 7.8	0.0004
LVEF, % (site read)	69 ± 5	67 ± 5	64 ± 5	−5 ± 6	<0.0001
Resting LVOT gradient (site read)	52 ± 33	17 ± 18	12 ± 10	−40 ± 34	<0.0001
Valsalva LVOT gradient (site read)	81 ± 35	37 ± 25	28 ± 21	−53 ± 39	<0.0001

Values are mean ± SD, unless otherwise indicated.
LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; other abbreviations as in Table 1.

42 weeks of treatment (week 48 mean value: 12 ± 10 mm Hg; change from baseline: −40 ± 34 mm Hg; $P < 0.0001$). Similarly, Valsalva LVOT gradient declined by 50% from 81 ± 35 mm Hg to 41 ± 24 mm Hg. By 48 weeks, there was a modest further reduction by an additional 16% such that the mean Valsalva LVOT gradient was 28 ± 21 mm Hg, representing an overall 65.5% relative reduction and absolute −53 ± 39 mm Hg ($P < 0.0001$) change from baseline (Central Illustration B, Table 2). At week 48, a complete hemodynamic response, defined as below-threshold resting and Valsalva gradients (<30 mm Hg and <50 mm Hg, respectively), was observed in 81.2% of participants (n = 37).

Mean LVEF remained within normal limits throughout the study period (Central Illustration C, Table 2). Consistent with the mechanism of action of aficamten, there was a modest decline in LVEF to 64% ± 5% at week 48 (change from baseline: −5% ± 6%; $P < 0.0001$) (Central Illustration D).

DIASTOLIC FUNCTION. Participants demonstrated major reduction in echocardiographic measures of diastolic dysfunction over the 48-week study period (Figure 1, Table 2). Aficamten treatment was associated with reduction in lateral and septal E/e′ (change from baseline to week 48: −2.2 ± 6.1; $P = 0.02$; and −2.6 ± 5.4; $P = 0.002$, respectively), with a parallel decrease in left atrial volume index (change from baseline to week 48: −3.5 ± −6.6 mL/m^2; $P < 0.001$) (Table 2).

STRUCTURAL CHANGES. The maximal wall thickness decreased (change from baseline to week 48: −1.2 ± 1.6 mm; $P < 0.0001$) (Figure 1). The left ventricular end-systolic volume increased over time (change from baseline to week 48: 4.6 ± 7.8 mL; $P < 0.001$), whereas there was no change in the left ventricular end-diastolic volume (change from baseline to week 48: 0.2 ± 12.4 mL; $P = 0.92$) (Table 2).

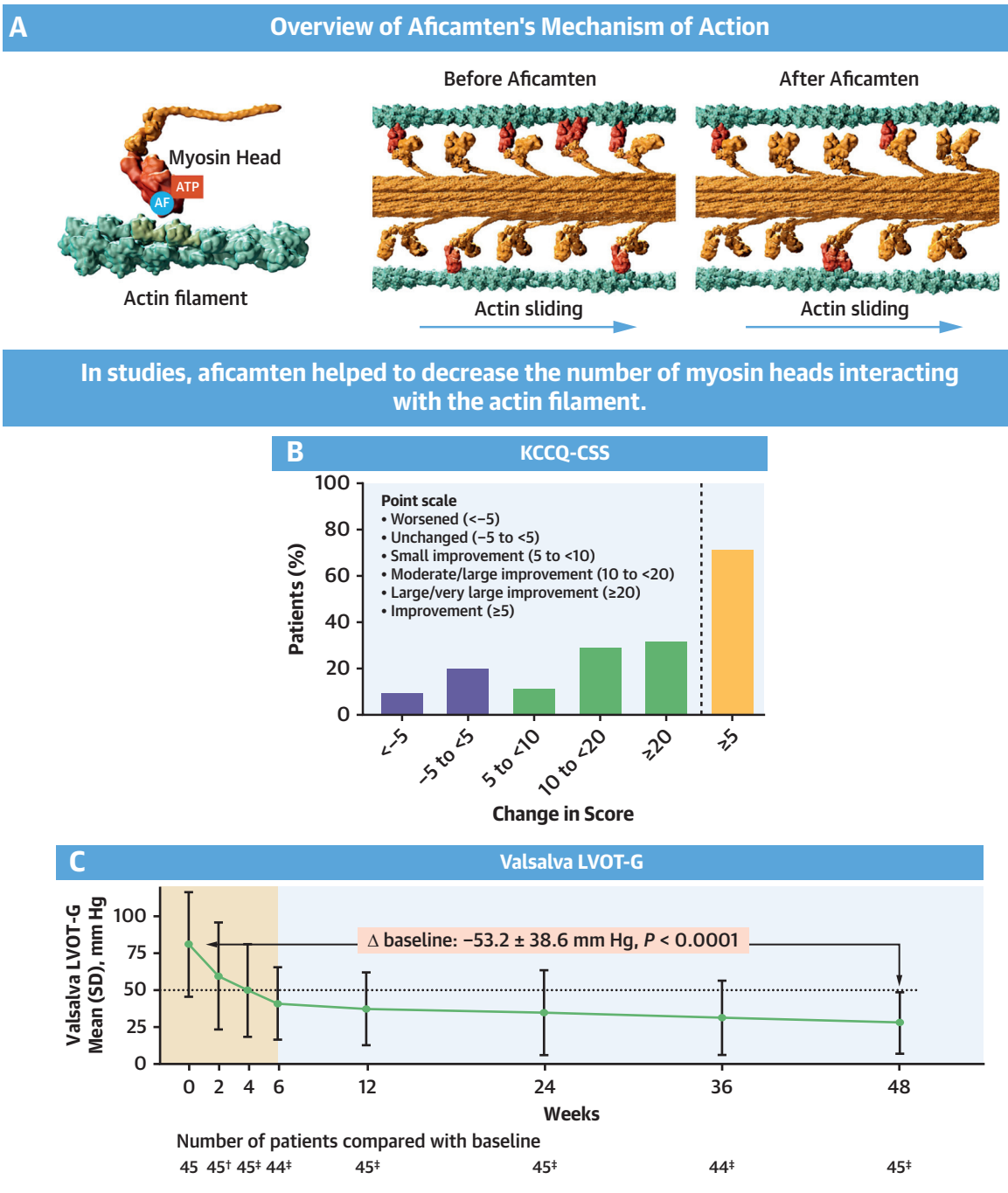
SYMPTOM BURDEN. Aficamten treatment was associated with substantial improvements in symptom burden, with 80% of participants (n = 36) having ≥1 NYHA functional class improvement as early as 12 weeks after treatment and maintained thereafter (Figure 2). Aficamten treatment resulted in a 7-fold reduction in the number of participants experiencing NYHA functional class III symptoms at 48 weeks (n = 3) compared with baseline (n = 22). Although no participants experienced NYHA functional class I symptoms at baseline, after 48 weeks of

TABLE 3 Treatment-Emergent Adverse Events and Events of Special Interest (N = 46)

	n (%)	Number of Events
Patients with ≥1 TEAE	41 (89.1)	161
Patients with TESAEs	4 (8.7)	5
Patients with fatal TEAEs	0 (0)	0
Patients with TEAEs leading to drug interruption[a]	1 (2.2)	1
Patients with TEAEs leading to dose reduction[b]	2 (4.3)	2
Patients with AEs related to study drug (per investigator)	10 (21.7)	15
LVEF <50%	2 (4.3)	2
LVEF <50% with heart failure	0 (0)	0
New-onset atrial fibrillation	0 (0)	0
Recurrent atrial fibrillation	2 (4.3)	2

[a]1 patient with persistent atrial fibrillation requiring cardioversion and rhythm control interrupted treatment for 44 days and then successfully restarted. [b]1 patient with reduced ejection fraction had dose reduction from 15 to 10 mg and 1 patient with QT prolongation on electrocardiogram (not confirmed by core laboratory) had dose reduction from 10 to 5 mg, which was not protocol-guided.
AE = adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; other abbreviation as in Table 1.

CENTRAL ILLUSTRATION **Efficacy of Long-Term Treatment With Aficamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy Patients With Up to 48 Weeks of Follow-Up**



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(A) Schema of aficamten mechanism of action: aficamten reduces the number of actin-myosin cross bridges within the sarcomere. (B) Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS). (C) Valsalva left ventricular outflow tract gradient (LVOT-G). (D) Left ventricular ejection fraction (LVEF). (E) N-terminal pro-B-type natriuretic peptide (NT-proBNP). *$P < 0.01$; †$P < 0.001$; ‡$P < 0.0001$. AF = aficamten; ATP = adenosine triphosphate; CV = coefficient of variation.

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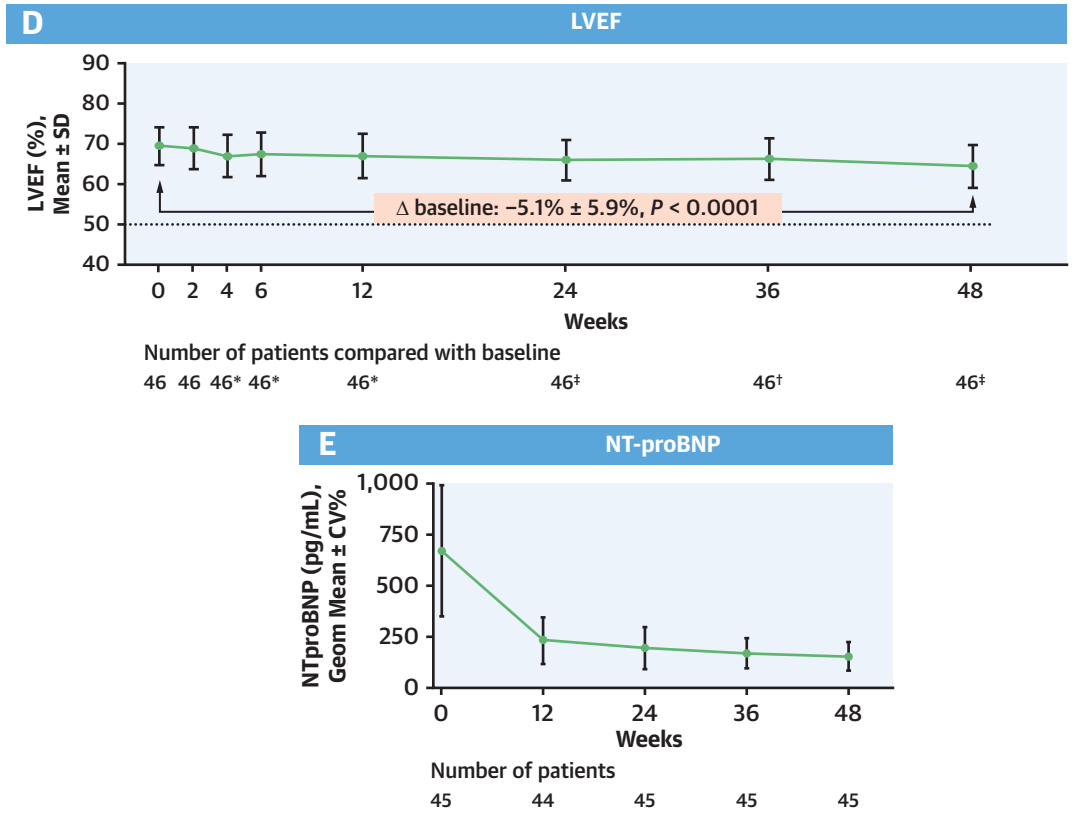
CENTRAL ILLUSTRATION Continued



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aficamten treatment, 24 participants (51.1%) were classified as such. Similarly, there was an early and sustained improvement in patient-reported outcomes. The mean KCCQ-CSSs improved by 18% from baseline to week 48 (73.0 ± 18 to 86 ± 15; mean change: 13 ± 17; $P < 0.0001$). By week 48, 32 (71%) and 14 (31%) of the 45 participants had ≥5-point (small) and ≥20-point (large) improvement in KCCQ-CSS, respectively (Central Illustration D).

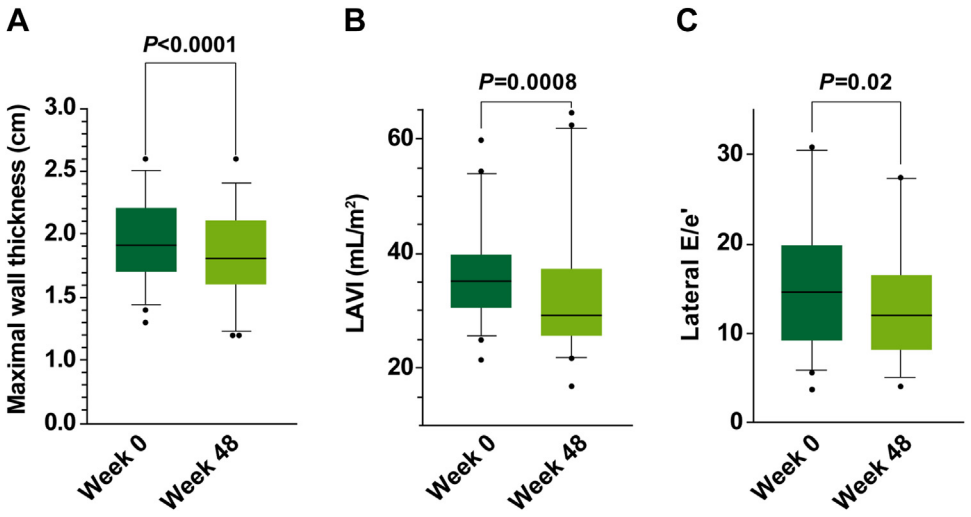
CARDIAC BIOMARKERS. Similar to the observed hemodynamic and symptom improvements, aficamten treatment resulted in an early and sustained decrease in cardiac biomarkers of wall stress and myocardial injury. NT-proBNP was reduced by 63% (95% CI: 51%-75%; $P < 0.0001$) from baseline to week 48 (Central Illustration E). The reduction in hs-cTnI was less rapid, but progressively decreased in a linear fashion over time by 24% (95% CI: 8%-39%; $P = 0.0031$) at week 48 (Figure 3).

SEPTAL REDUCTION THERAPY ELIGIBILITY. Nineteen participants (41%) met guideline-defined septal reduction therapy (SRT) eligibility criteria (NYHA functional class III symptoms and LVOT gradient ≥50 mm Hg despite optimal medical therapy) at baseline. Only 1 participant remained eligible by both criteria after just 6 months of treatment with aficamten, representing a reduction in guideline eligibility for SRT by 95%.

DISCUSSION

This analysis from FOREST-HCM contains comprehensive data from the first cohort of oHCM patients to finish 48 weeks of aficamten treatment, translating to 86.6 patient-years of exposure. We show the following: 1) aficamten treatment effectively reduces LVOT gradient and relieves symptoms, and subsequently almost all participants who were guideline-eligible for SRT at the start of the study were no longer eligible after just 6 months of therapy and remained so at 48 weeks; 2) dose selection driven by the treating physician's interpretation of the echocardiogram with integration of the clinical picture is effective; and 3) aficamten treatment remains safe with a low incidence of LVEF excursions to <50%,

FIGURE 1 Cardiac Structure and Diastolic Function at Baseline and Week 48

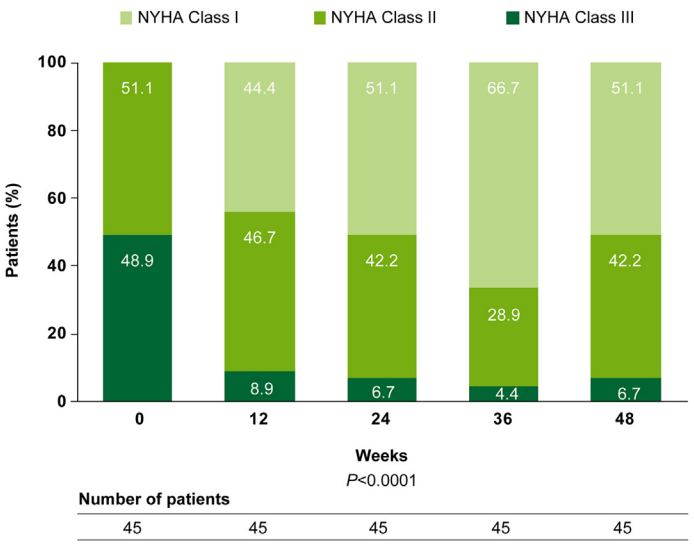


Change in maximal wall thickness (A), LAVI (B), and lateral E/e′ from baseline to 48 weeks (C). Efficacy of long-term treatment with aficamten on echocardiographic measures of cardiac structure and diastolic function over the 48-week study period. Mean and 95% CI in all panels. LAVI = left atrial volume index.

with no symptomatic heart failure events and no instances of new-onset atrial fibrillation.

At the time of this analysis, a large proportion of REDWOOD-HCM (45 of 54; 83.3%) and eligible SEQUOIA-HCM (168 of 190; 88.4%) participants were enrolled in FOREST-HCM. Participants treated with aficamten experienced substantial decrease in resting and Valsalva LVOT gradients, with mean values dropping below the threshold currently considered severe obstruction (any gradient >50 mm Hg). In addition, objective echocardiographic markers of diastolic dysfunction, abnormal cardiac structural remodeling, and cardiac biomarkers all showed marked reductions that were accompanied by meaningful progress in symptom burden and functional status. Importantly, 48-week treatment with aficamten appeared safe, with 2 of 46 occurrences (4.3%) of reversible and asymptomatic LVEF <50%, no instances of clinical heart failure or heart failure hospitalizations, no deaths, and no instances of new-onset atrial fibrillation.

FIGURE 2 Transition in NYHA Functional Class Over Time: Changes in NYHA Functional Class



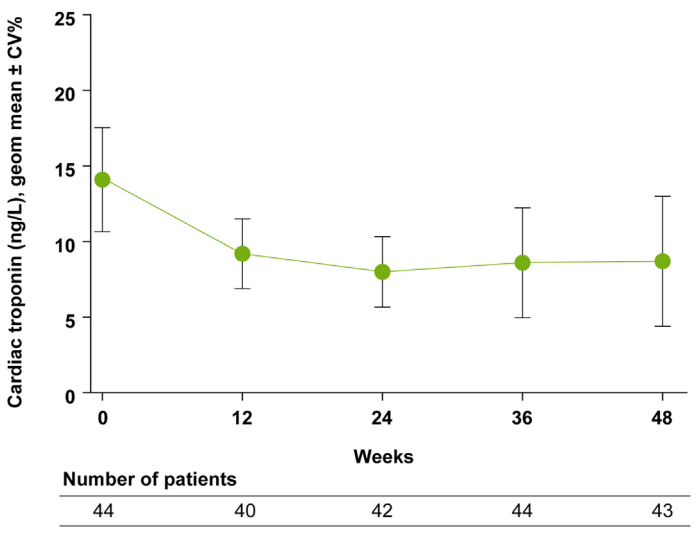
Efficacy of long-term treatment with aficamten on patients' NYHA functional class.

Direct comparisons of CMIs with guideline-recommended first-line therapies are lacking; however, data from the phase 3 MAPLE-HCM (Phase 3 Trial to Evaluate the Efficacy and Safety of Aficamten Compared to Metoprolol Succinate in Adults With Symptomatic oHCM; NCT05767346) trial evaluating the efficacy and safety of monotherapy aficamten compared with monotherapy metoprolol succinate in adults with symptomatic oHCM will address this question (participants from this study are also rolling over to FOREST-HCM). In a 2-week crossover trial (TEMPO-HCM [The Effect of Metoprolol on Myocardial Function, Perfusion, Hemodynamics and Heart

Failure Symptoms in Patients with Hypertrophic Obstructive Cardiomyopathy]) of metoprolol succinate vs placebo with 29 participants with symptomatic (NYHA functional class II-IV) oHCM, metoprolol succinate effectively lowered resting LVOT gradient (to 25 mm Hg; Q1-Q3: 15-58 mm Hg vs 72 mm Hg; Q1-Q3: 28-87 mm Hg with placebo), but did not demonstrate efficacy with respect to the Valsalva LVOT gradient (94 mm Hg; Q1-Q3: 40-144 mm Hg vs 119 mm Hg; Q1-Q3: 89-165 mm Hg, in the metoprolol and placebo cohorts, respectively), thus incompletely treating obstruction. Furthermore, most participants continued to be symptomatic.[19] The pharmacokinetics of metoprolol succinate do not suggest that a longer treatment period was needed to demonstrate a greater pharmacodynamic effect. Despite a reduction in resting LVOT gradient, treatment with metoprolol succinate had no effect on NT-proBNP. This contrasts with the decline in NT-proBNP noted with aficamten treatment. More patients in the FOREST-HCM study were highly symptomatic at baseline than in TEMPO-HCM (48% NYHA functional class III vs 38%); with metoprolol treatment, only 10% were deemed as achieving NYHA functional class I symptoms compared with 51% of those treated with aficamten. The pharmacodynamic target of aficamten is LVEF– with a goal of normalizing a hyperdynamic left ventricle. Metoprolol did not reduce LVEF and was associated with the known off-target side effects of beta-blockers, with 4 patients (14%) experiencing dizziness and fatigue resulting in dose reductions. Although exercise testing and peak oxygen uptake (pVO_2) are not tested in FOREST-HCM, as noted in SEQUOIA-HCM, aficamten treatment resulted in 1.7 mL/kg/min improvement in pVO_2 compared with placebo,[15] whereas metoprolol treatment had no meaningful impact on pVO_2 when compared with placebo.[20-23]

Symptom relief and hemodynamic improvements resulted in the expected transition of patients who were guideline eligible for SRT at baseline to no longer qualifying for SRT, with >90% of individuals achieving this criterion from baseline through week 48. Notably, there was a 7-fold reduction in the number of participants with the highest symptom burden (NYHA functional class III) after 48 weeks of aficamten treatment, a magnitude of improvement previously only seen with SRT.[24] Only 1 participant opted to proceed with myectomy due to persistent obstruction; 3 others were reported to have persistent severe functional impairment (NYHA functional class III) at week 48, but opted to remain on aficamten.

FIGURE 3 Change in High-Sensitivity Cardiac Troponin I Over Time



Efficacy of long-term treatment with aficamten on cardiac biomarker of myocardial injury. CV = coefficient of variation; geom mean = geometric mean.

This paradox may be due to several potential unmeasured or unreported factors. For example, NYHA functional class may be too blunt a tool to effectively capture within-class improvements, there may be specific patient aversion to invasive treatments, or there may not be adequate access to an experienced operator for SRT. Importantly, participants meeting the criteria for SRT were already receiving guideline-recommended therapies (beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide) and remained refractory to these medicines. Given the invasive nature of SRT and subsequent risk for serious complications, and limited access to high-quality SRT, the potential for aficamten to enable patients to avoid surgery is particularly encouraging.

Safety and efficacy of aficamten was assessed by echocardiogram for optimal dosing. Given the potential need for long-term treatment options for oHCM, pharmacologic treatments need to be safe and efficacious over long periods of time. Most TEAEs (91%) were mild or moderate in severity. Events of LVEF <50% and recurrent atrial fibrillation occurred with no greater frequency than previously reported in the parent studies, supporting long-term treatment safety.[8,9,15]

STUDY LIMITATIONS. The findings should be interpreted in the context of important limitations. First,

the single-arm active treatment design of this study can introduce bias, especially when reporting subjective outcomes (eg, NYHA functional class, KCCQ). However, the results are consistent with the findings from parent randomized, placebo-controlled studies, and are consistent with other objective data reported (LVOT gradient and biomarkers). Second, this cohort is relatively small. FOREST-HCM is an ongoing study from which future analyses will generate larger numbers of treated patients; however, the current analysis represents the largest cohort achieving nearly 1 years' worth of exposure. Third, these results are from participating investigators and centers with expertise in HCM care, and the generalizability of echocardiographic interpretations may not apply to all centers.

CONCLUSIONS

The cumulative results from this 48-week analysis of patients with symptomatic oHCM from FOREST-HCM demonstrate that dose selection integrating echocardiographic parameters and clinical judgment mimicking what would be expected postapproval, appears both safe and effective. There continues to be a low incidence of LVEF <50% excursions, all of which were clinically silent. There were no instances of new-onset atrial fibrillation. Furthermore, aficamten treatment appeared to allow almost all participants, who would nominally be considered for SRT, to effectively avoid an invasive procedure for at least 1 year. Finally, the clinical benefits of aficamten therapy appear to enable advantageous structural remodeling, which could potentially translate to disease modification.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Aficamten targets the hypercontractility underlying the development of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. Aficamten has been shown to be effective in improving left ventricular outflow obstruction, exercise capacity, symptom burden, and health status, and biomarkers of wall stress and myocardial injury after 24 weeks of treatment in patients with oHCM in the SEQUOIA-HCM study. The ongoing FOREST-HCM study is evaluating longer-term safety and efficacy of aficamten treatment.

TRANSLATIONAL OUTLOOK: This 48-week analysis from the cohort of patients with oHCM participating in FOREST-HCM provides an assessment of 86.6 patient-years of exposure. Longer-term treatment with aficamten with dose selection integrating echocardiographic parameters and clinical judgment appears safe and effective. The ongoing FOREST-HCM study is projected to be the largest study of patients with HCM treated with aficamten and will provide valuable efficacy and safety information.

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