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Circulation: Heart Failure

ORIGINAL ARTICLE

# Effect of Aficamten in Women Compared With Men With Obstructive Hypertrophic Cardiomyopathy in SEQUOIA-HCM

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**BACKGROUND:** Women with obstructive hypertrophic cardiomyopathy often present with a greater burden of disease and worse prognosis. Whether there are sex-related differences in response to aficamten is unknown.

**METHODS:** We performed a prespecified subgroup analysis of sex differences in the double-blind, randomized-controlled SEQUOIA-HCM trial (Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM) of aficamten versus placebo in patients with obstructive hypertrophic cardiomyopathy. Baseline characteristics were compared using the *t* test for continuous variables and the $\chi^2$ test for categorical variables. Prespecified primary (change in peak oxygen uptake) and secondary end points from baseline to end of treatment (week 24) were analyzed using linear regression models, adjusted for baseline values, β-blocker use, and exercise mode.

**RESULTS:** Of the 282 participants, women (n=115) were older (64 years in women versus 56 years in men) and had lower Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, higher NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, and lower peak oxygen uptake at baseline. Women had smaller left ventricular chamber sizes, higher E/e' ratios, and higher left ventricular outflow tract gradients. At 24 weeks, there was a significant treatment-related increase in peak oxygen uptake in women (+1.5 [+0.7 to +2.4]) and men (+2.0 [+0.9 to +3.0]). Both women and men had significant treatment-related decreases in left ventricular outflow tract gradients at rest and with Valsalva, with no sex-by-treatment interaction at week 24 ($P_{interaction}$≥0.13). There was a significant improvement in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score in women (11 [6–15]) and men (6 [2–9]; $P_{interaction}$=0.08). Women had a greater reduction in lateral E/e' ratio ($P_{interaction}$=0.01). The geometric mean proportional reduction in NT-proBNP was similar in women and men ($P_{interaction}$=0.10).

**CONCLUSIONS:** Women enrolled in SEQUOIA-HCM were older with worse baseline health status, higher NT-proBNP, and higher left ventricular outflow tract gradients compared with men. Despite these differences, both men and women derived significant benefits in the primary and secondary end points following treatment with aficamten.

**Key Words:** cardiomyopathy, hypertrophic ■ echocardiography ■ heart failure ■ hypertrophy ■ sex characteristics

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## WHAT IS NEW?

- In the SEQUOIA-HCM trial (Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM) evaluating the safety and efficacy of aficamten in patients with obstructive hypertrophic cardiomyopathy, women were older with worse heart failure and patient-reported health status.
- Women with symptomatic obstructive hypertrophic cardiomyopathy had worse measures of diastolic function and higher left ventricular outflow tract gradients at rest and with Valsalva.
- Treatment with aficamten for 24 weeks was associated with similar improvement in the primary end point (change in peak oxygen uptake by cardiopulmonary exercise test) in women and men.
- After 24 weeks, women and men derived similar benefits in prespecified secondary end points.

## WHAT ARE THE CLINICAL IMPLICATIONS?

- There are sex-related clinical and echocardiographic differences in symptomatic obstructive hypertrophic cardiomyopathy. Sex-specific diagnostic criteria may be appropriate.
- Aficamten is safe and effective in both women and men, and should be offered as an option for treatment of symptomatic obstructive hypertrophic cardiomyopathy.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **EXPLORER-HCM** | Clinical Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy |
| **FOREST-HCM** | Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Aficamten in Adults With HCM |
| **HCM** | hypertrophic cardiomyopathy |
| **KCCQ-CSS** | Kansas City Cardiomyopathy Questionnaire Clinical Summary Score |
| **LV** | left ventricular |
| **LVEF** | left ventricular ejection fraction |
| **LVOT** | left ventricular outflow tract |
| **NT-proBNP** | N-terminal pro-B-type natriuretic peptide |
| **NYHA** | New York Heart Association |
| **$pVO_2$** | peak oxygen uptake |
| **SEQUOIA-HCM** | Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM |

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic disorders of the heart and is characterized by left ventricular (LV) hypertrophy without another underlying cardiac or systemic disease process to explain the hypertrophy.[1,2] Obstructive HCM, defined as a peak LV outflow tract (LVOT) gradient of ≥30 mm Hg, affects more than two-thirds of individuals with HCM and is associated with worse outcomes, such as symptomatic heart failure, arrhythmias, and mortality including sudden cardiac death.[1,2]

Traditionally, management of LVOT obstruction involves medical therapies (β-blockers, nondihydropyridine calcium channel blockers, and, more recently, cardiac myosin inhibitors) and septal reduction therapy (surgical septal myectomy or alcohol septal ablation) in those who have marked symptoms and persistent LVOT gradient elevation despite medical treatment.[1,2] In those requiring septal reduction therapy, procedural risks remain even in high-volume centers. Aficamten is an investigational, next-in-class cardiac myosin inhibitor that decreases the number of actin-myosin cross-bridges within cardiac sarcomeres, thereby decreasing LV contractility and reducing LVOT obstruction.[3] In SEQUOIA-HCM (Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; Unique identifier: NCT05186818), aficamten compared with placebo led to significant improvements in peak oxygen uptake, symptoms, and health status and reductions in LVOT gradients at rest and with Valsalva maneuver at 24 weeks.[3] Mavacamten, a first-in-class cardiac myosin inhibitor, showed improvement in exercise capacity and LVOT obstruction in EXPLORER-HCM (Clinical Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; Unique identifier: NCT03470545).[4]

Previous analyses have demonstrated worse prognosis in women with HCM, such as a higher likelihood of progressing to advanced heart failure and higher risks of mortality.[5,6] In addition to differences in presentation and outcomes, women may also respond differently to HCM therapies. In a prespecified subgroup analysis of EXPLORER-HCM, women had similar improvement in exercise capacity and had greater improvements in health status and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels.[7] However, whether women and men derive similar benefits from aficamten is unknown.

In this prespecified subgroup analysis, we evaluated sex differences in baseline clinical characteristics, treatment response, and adverse events associated with aficamten. We further evaluated sex-related differences in echocardiographic parameters and changes in echocardiographic characteristics in response to aficamten in SEQUOIA-HCM.

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# METHODS

## Date Availability Statement

Qualified researchers may submit a request containing the research objectives, end points or outcomes of interest, a statistical analysis plan, data requirements, a publication plan, and qualifications of the researcher(s). Requests are reviewed by a committee of internal and external advisors. If approved, information necessary to address the research question will be provided under the terms of a data-sharing agreement. Data-sharing requests will be considered after applications for marketing authorization in the United States and Europe have been reviewed and final decisions rendered. There is no end date for eligibility to submit a data-sharing request for this study. Requests may be submitted to medicalaffairs@cytokinetics.com.

## Study Design

SEQUOIA-HCM was a phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial in patients with symptomatic obstructive HCM. A detailed study design has been previously published.[3,8] Briefly, 282 patients aged 18 to 85 years with HCM (LV hypertrophy with nondilated LV chamber in the absence of other cardiac disease, LV wall thickness ≥15 mm in at least 1 myocardial segment, or ≥13 mm with known genetic mutation or family history of HCM), LV ejection fraction (LVEF) ≥60%, evidence of LVOT obstruction (resting LVOT gradient ≥30 mm Hg and LVOT gradient with Valsalva ≥50 mm Hg), New York Heart Association (NYHA) functional class II or III, and peak oxygen uptake ($pVO_2$) ≤90% predicted at screening were randomized to receive aficamten or placebo. Patients were followed for a 24-week treatment period followed by 4 weeks of washout at the end of the trial.[8]

The study protocol was reviewed and approved by an institutional review board at each trial site. All participants provided written informed consent, and the trial was conducted in accordance with the Declaration of Helsinki and with the International Council for Harmonization Good Clinical Practice guidelines.

## Study Outcomes

The primary end point was change in $pVO_2$ by cardiopulmonary exercise test from baseline to week 24.[3,8] Key secondary end points included changes in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) from baseline to week 12 and week 24; an improvement of at least 1 NYHA functional class from baseline to week 12 and week 24; change in post-Valsalva LVOT gradients from baseline to week 12 and week 24; and proportion of patients with post-Valsalva LVOT gradient <30 mm Hg at week 12 and week 24.[8] The key exploratory end point was the geometric mean proportional change in NT-proBNP. A full list of secondary and exploratory end points has been previously published.[8]

## Study Procedures

Among 543 patients screened, 282 were randomized in a 1:1 fashion to receive a placebo or aficamten. Aficamten was started at 5 mg and escalated every 2 weeks within the first 6 weeks, by 5-mg increments (10, 15, and 20 mg), to achieve a Valsalva LVOT gradient <30 mm Hg while maintaining an LVEF ≥50% based on site interpretations. Doses were maintained until week 24, followed by a 4-week washout period.

Resting echocardiograms were performed at screening, day 1, and weeks 2, 4, 6, 8, 12, 16, 20, 24 (end of treatment), and 28 (end of study). Echocardiograms performed for weeks 2, 4, 6, and 8 were limited protocol and for medication titration purposes. Echocardiograms were performed at study sites by certified sonographers using a prespecified protocol. Images were evaluated and quantified by the Cardiovascular Imaging Core Laboratory (Brigham and Women's Hospital, Boston, MA) in a blinded fashion. Measurements were obtained following the American Society of Echocardiography recommendations and previously published.[9]

## Statistical Analysis

Clinical and echocardiographic characteristics (including baseline and changes from baseline to 24 weeks) were reported as mean±SD for continuous variables, except for NT-proBNP and high-sensitive troponin, which were reported as medians and interquartile ranges. Categorical variables were reported as numbers and percentages. Baseline clinical and echocardiographic characteristics were compared using the *t* test for continuous variables and the $\chi 2$ test for categorical variables. Changes from baseline to 24 weeks were analyzed using linear regression models, adjusted for baseline values, β-blocker use, and exercise mode (bicycle versus treadmill). No adjustments were made for multiple comparisons, and *P* values of <0.05 were considered statistically significant. Analyses were performed using STATA (version 16.0; College Station, TX).

# RESULTS

## Baseline Clinical Characteristics in Men and Women

Among the 282 participants, 115 (41%) were women. Compared with men, women were older (mean age, 64±11 years in women versus 56±13 years in men; *P*<0.001) but had similar comorbidities (Table 1). Women had higher NT-proBNP levels, lower baseline $pVO_2$, and worse health status (KCCQ-CSS 70±19 in women versus 78±16 in men; *P*<0.001) and were more likely to have NYHA class III symptoms. Women had a lower rate of implantable defibrillators (Table 1).

## Baseline Echocardiographic Parameters in Men and Women

At baseline, women had higher LVOT gradients at rest and with the Valsalva maneuver (Table 1). Women also had lower maximum wall thickness, lower LV mass index, and smaller LV chamber size (Table 1). In terms of LV systolic function, women and men had similar LVEF (75% in women versus 74% in men) and absolute LV global longitudinal strain (15.9% in women and 15.3% in men). Measures of RV systolic function were also similar between women and men (Table 1).

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**Table 1. Baseline Clinical Characteristics in Men and Women in SEQUOIA-HCM**

| | Women (n=115) | Men (n=167) | *P* value |
|---|---|---|---|
| Randomized to active treatment | 56 (49%) | 86 (52%) | 0.64 |
| Age, y | 64±11 | 56±13 | <0.001 |
| Race | | | 0.29 |
| White | 95 (83%) | 128 (77%) | |
| Asian | 18 (16%) | 36 (22%) | |
| Black | 2 (1.7%) | 1 (0.6%) | |
| Other | 0 (0.0%) | 2 (1.2%) | |
| Geographic region | | | 0.21 |
| China | 16 (14%) | 30 (18%) | |
| North America | 45 (39%) | 49 (29%) | |
| Rest of the world | 54 (47%) | 88 (53%) | |
| Medical history | | | |
| Hypertension | 64 (56%) | 81 (49%) | 0.24 |
| Known HCM-causing gene mutation | 21 (18%) | 28 (17%) | 0.74 |
| Positive family history of HCM | 34 (30%) | 41 (25%) | 0.35 |
| Paroxysmal atrial fibrillation | 15 (13%) | 26 (16%) | 0.55 |
| Permanent atrial fibrillation | 1 (1%) | 2 (1%) | 0.79 |
| Coronary artery disease | 11 (10%) | 24 (14%) | 0.23 |
| Diabetes | 10 (9%) | 13 (8%) | 0.78 |
| Vital signs | | | |
| Systolic blood pressure, mm Hg | 124±17 | 126±15 | 0.31 |
| Diastolic blood pressure, mm Hg | 72±10 | 76±10 | <0.001 |
| Rest heart rate, beats/min | 70±12 | 69±13 | 0.40 |
| BMI, kg/m$^2$ | 27.8±4.0 | 28.3±3.5 | 0.22 |
| Background HCM therapy | | | |
| β-Blocker use | 63 (55%) | 110 (66%) | 0.06 |
| Calcium channel blocker | 47 (41%) | 50 (30%) | 0.06 |
| Disopyramide | 15 (13%) | 21 (13%) | 0.91 |
| Implantable cardioverter defibrillator | 9 (8%) | 30 (18%) | 0.015 |
| NYHA class at baseline | | | <0.001 |
| Class II | 74 (64%) | 140 (84%) | |
| Class III | 40 (35%) | 27 (16%) | |
| Class IV | 1 (1%) | 0 (0%) | |
| Baseline KCCQ-CSS | 70±19 | 78±16 | <0.001 |
| NT-proBNP, pg/mL | 1104 (510–2216) | 562 (283–1333) | <0.001 |
| High-sensitivity troponin I, ng/L | 10 (6–17) | 15 (8–38) | <0.001 |
| Cardiopulmonary exercise testing | | | |
| CPET modality: bicycle | 53 (46%) | 74 (44%) | 0.77 |
| Total workload, W | 97±35 | 140±35 | <0.001 |
| % of predicted oxygen uptake | 56.9±11.9 | 56.8±11.9 | 0.93 |
| $pVO_2$, mL/kg per min | 16.0±3.6 | 20.2±4.2 | <0.001 |
| Peak respiratory exchange ratio | 1.18±0.10 | 1.18±0.10 | 1.00 |
| Echocardiographic parameters | | | |
| LVOT gradients | | | |
| LVOT gradient, rest, mm Hg | 61±31 | 52±28 | 0.010 |
| LVOT gradient, Valsalva, mm Hg | 90±32 | 79±32 | 0.005 |
| LV structure and systolic function | | | |
| Maximal wall thickness, mm | 20.3±2.6 | 21.3±3.2 | 0.011 |

(*Continued*)

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**Table 1. Continued**

| | Women (n=115) | Men (n=167) | *P* value |
|---|---|---|---|
| Interventricular septum, mm | 18.9±3.0 | 19.3±3.2 | 0.20 |
| Inferolateral wall, mm | 12.6±2.8 | 13.0±2.8 | 0.33 |
| LV mass index, g/m² | 126.2±30.0 | 136.1±36.0 | 0.016 |
| LVEDVi, mL/m² | 31.8±6.4 | 38.8±8.6 | <0.001 |
| LVESVi, mL/m² | 7.8±2.3 | 10.0±3.7 | <0.001 |
| LVEF, % | 75.3±6.0 | 74.4±5.7 | 0.21 |
| GLS, % | 15.5±2.9 | 15.3±3.4 | 0.67 |
| LV diastolic function | | | |
| LA volume index, mL/m² | 41.7±15.3 | 39.6±12.8 | 0.22 |
| LA width, mm | 40.1±5.6 | 42.9±5.9 | <0.001 |
| Peak E wave velocity, cm/s | 88.9±32.7 | 82.0±25.0 | 0.045 |
| Peak A wave velocity, cm/s | 94.2±30.7 | 74.6±24.5 | <0.001 |
| E/A ratio | 1.0±0.5 | 1.2±0.6 | 0.007 |
| Lateral e' velocity, cm/s | 5.4±1.9 | 6.5±2.2 | <0.001 |
| Septal e' velocity, cm/s | 4.2±1.2 | 4.9±1.6 | <0.001 |
| Lateral E/e' | 18.2±8.5 | 13.9±6.3 | <0.001 |
| Septal E/e' | 22.9±9.8 | 18.0±7.5 | <0.001 |
| RV systolic function | | | |
| TAPSE, mm | 21.1±3.6 | 21.3±4.6 | 0.77 |
| RV s' velocity, cm/s | 13.0±2.6 | 12.8±2.4 | 0.49 |

Values represent mean±SD, n (%), or median (interquartile range). BMI indicates body mass index; CPET, cardiopulmonary exercise test; GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LA, left atrium; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; $pVO_2$, peak oxygen uptake; RV, right ventricle; SEQUOIA-HCM, Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; and TAPSE, tricuspid annular plane systolic excursion.

There were significant sex differences in measures of diastolic parameters. Women had higher E wave and A wave velocities. Women also had lower lateral e' velocities (5.4±1.9 cm/s in women versus 6.5±2.2 cm/s in men; $P<0.001$) and septal e' velocities (4.2±1.2 cm/s in women versus 4.9±1.6 cm/s in men; $P<0.001$; Table 1). Lateral and septal E/e' ratios were also higher in women compared with men (Table 1).

## Treatment Effect of Aficamten on Primary End Point

Compared with participants in the placebo arm, women and men treated with aficamten had an improvement in $pVO_2$ of 1.5 (95% CI, 0.7–2.4) and 2.0 (95% CI, 0.9–3.0) mL/kg per min, respectively (Table 2). There was no significant sex-by-treatment interaction ($P_{interaction}=0.51$; Table 2). The number of data points available for primary and secondary end points is provided in Table S1.

## Treatment Effect of Aficamten on Secondary and Exploratory End Points

At 24 weeks, treatment with aficamten was associated with an 11-point increase in KCCQ-CSS in women (95% CI, 6–15) and a 6-point increase in KCCQ-CSS in men (95% CI, 2–9; $P_{interaction}=0.08$; Table 2; Figure 1). At week 12 and week 24, similar proportions of women and men had improvement of ≥1 NYHA functional class and LVOT gradient <30 mm Hg with Valsalva due to treatment with aficamten (Table 2). At week 12, compared with men, women treated with aficamten had a greater reduction in LVOT gradient with Valsalva ($P_{interaction}=0.003$; Table 2). However, at week 24, there were no significant sex differences in aficamten-related reduction in LVOT gradient with Valsalva ($P_{interaction}=0.13$) or total workload on cardiopulmonary exercise test ($P_{interaction}=0.65$).

Compared with those in the placebo group, women and men treated with aficamten had similar geometric mean proportional change of NT-proBNP: −84% (−79% to −87%) in women and −78% (−73% to −82%) in men ($P_{interaction}=0.10$; Table 2; Figure 1). Women and men also had similar geometric mean proportional change of high-sensitivity troponin I: −47% (−36% to −57%) in women and −41% (−31% to −49%) in men ($P_{interaction}=0.37$; Figure 1). Further details on sex differences in clinical outcomes in the placebo group and the aficamten group are shown in Tables S2 and S3, respectively.

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**Table 2. Primary and Secondary End Points in Men and Women in SEQUOIA-HCM**

| | Women (N=115) | | | Men (N=167) | | | |
|---|---|---|---|---|---|---|---|
| | Mean Δ placebo (n=59) | Mean Δ aficamten (n=56) | Treatment effect | Mean Δ placebo (n=81) | Mean Δ ficamten (n=86) | Treatment effect | Sex-by-treatment $P_{interaction}$ |
| Primary end point: peak $VO_2$ at 24 wk, mL/kg per min | −0.1±2.4 | +1.4±2.3 | +1.5 (+0.7 to +2.4) | +0.1±3.0 | +2.0±3.6 | +2.0 (+0.9 to +3.0) | 0.51 |
| Secondary end points: | | | | | | | |
| KCCQ-CSS at week 24 | +6.1±12.3 | +14.7±14.9 | +11 (+6 to +15) | +4 (+1 to +6) | +9.4±11.6 | +6 (+2 to +9) | 0.08 |
| Improvement of ≥1 NYHA functional class at week 24 | 15 (25.4%) | 30 (53.6%) | 29.5% (11.9% to 47.1%) | 19 (23.5%) | 53 (61.6%) | 38.0% (23.8% to 52.1%) | 0.44 |
| LVOT gradient after Valsalva at week 24, mm Hg | −1.9±37.9 | −59.6±35.6 | −56 (−67 to −44) | 4 (−3 to 12) | −39.8±36.6 | −46 (−54 to −38) | 0.13 |
| LVOT gradient of <30 mm Hg after Valsalva at week 24 | 2 (3.4%) | 32 (57.1%) | 52.2% (38.3% to 66.1%) | 3 (3.7%) | 38 (44.2%) | 41.2% (29.4% to 52.9%) | 0.23 |
| Total duration of septal reduction therapy eligibility during treatment period, d | 110±59 | 32±18 | −78 (−108 to −48) | 123±46 | 42±34 | −76 (−110 to −41) | 0.97 |
| KCCQ-CSS at week 12 | +6.6±9.6 | +13.0±15.2 | +8 (+4 to +12) | +4 (+1 to +6) | +9.8±11.6 | +6 (+3 to +9) | 0.52 |
| Improvement of ≥1 NYHA functional class at week 12 | 13 (22.0%) | 22 (39.3%) | 20.5% (4.1% to 36.9%) | 12 (14.8%) | 47 (54.7%) | 38.7% (25.3% to 52.1%) | 0.08 |
| LVOT gradient after Valsalva at week 12, mm Hg | +4.8±33.7 | −56.7±32.5 | −60 (−70 to −49) | +1 (−6 to +8) | −36.7±36.1 | −40 (−48 to −31) | 0.003 |
| LVOT gradient of <30 mm Hg after Valsalva at week 12 | 3 (5.1%) | 33 (58.9%) | 52.6% (38.3% to 66.9%) | 5 (6.2%) | 41 (47.7%) | 41.4% (29.1% to 53.7%) | 0.22 |
| Total workload during CPET at week 24, W | −1.2±16.6 | +8.6±16.0 | +10.2 (+4.0 to +16.3) | +3.3 (−2.2 to +8.8) | +17.7±31.6 | +12.7 (+3.8 to +21.6) | 0.65 |
| Exploratory end point | | | | | | | |
| Geometric mean proportional change in NT-proBNP at week 24 | +2% (−25% to +22%) | −85% (−67% to −91%) | −84% (−79% to −87%) | −0% (−30% to +29%) | −77% (−67% to −89%) | −78% (−73% to −82%) | 0.10 |

Values represent mean change±SD, n (%), or median (interquartile range). The treatment effect is displayed as the mean change from baseline and 95% CI. Treatment effect and sex-by-treatment $P_{interaction}$ included baseline values, β-blocker use, and exercise modality as covariates. CPET indicates cardiopulmonary exercise test; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SEQUOIA-HCM, Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM; and $VO_2$, oxygen uptake.

## Treatment Effect of Aficamten on Echocardiographic Parameters

At 24 weeks, both men and women had reductions in LVOT gradients at rest and with Valsalva. In women, the placebo-corrected treatment effect of LVOT gradient at rest was −45 (95% CI, −54 to −35) mm Hg compared with −36 (95% CI, −43 to −28) mm Hg in men. The placebo-corrected treatment effect of LVOT gradient with Valsalva was −56 (95% CI, −67 to −44) mm Hg in women compared with −46 (95% CI, −54 to −38) mm Hg in men. Sex did not modify the treatment effect of aficamten on LVOT gradients ($P_{interaction}$=0.13 for both; Table 3; Figure 2).

In terms of LV structure, treatment with aficamten resulted in reductions in maximum wall thickness and LV mass index in both women and men (Table 3). Treatment with aficamten did not result in significant changes in LV end-diastolic volume index but led to an increase in LVESV index. Sex did not modify the treatment effect of aficamten on these parameters ($P_{interaction}$>0.2 for all echocardiographic parameters; Table 3).

Treatment with aficamten resulted in a similar reduction in LVEF ($P_{interaction}$=0.77) in women and men. In women, LVEF decreased by 4.4% (95% CI, 1.8%–7.1%) at week 24 compared with 4.9% (95% CI, 3.0%–6.8%) in men (Table 3; Figure 2). There were no significant treatment-related changes in absolute LV global longitudinal strain. Treatment with aficamten was also associated with reductions in TAPSE and RV S' velocities, and the reductions were similar in men and women (Table 3; $P_{interaction}$≥0.16 for both parameters).

For measures of diastolic function, treatment with aficamten resulted in an increase in lateral e' velocities and reductions in lateral and septal E/e' ratios. A greater reduction in lateral E/e' ratios was observed in women (−5.4 [95% CI, −7.2 to −3.5]) compared with men (−2.8 [95% CI, −4.1 to −1.5]; $P_{interaction}$=0.013; Table 3; Figure 2). Both women and men treated with aficamten had improved LV diastolic function measures over time (Figure 3).

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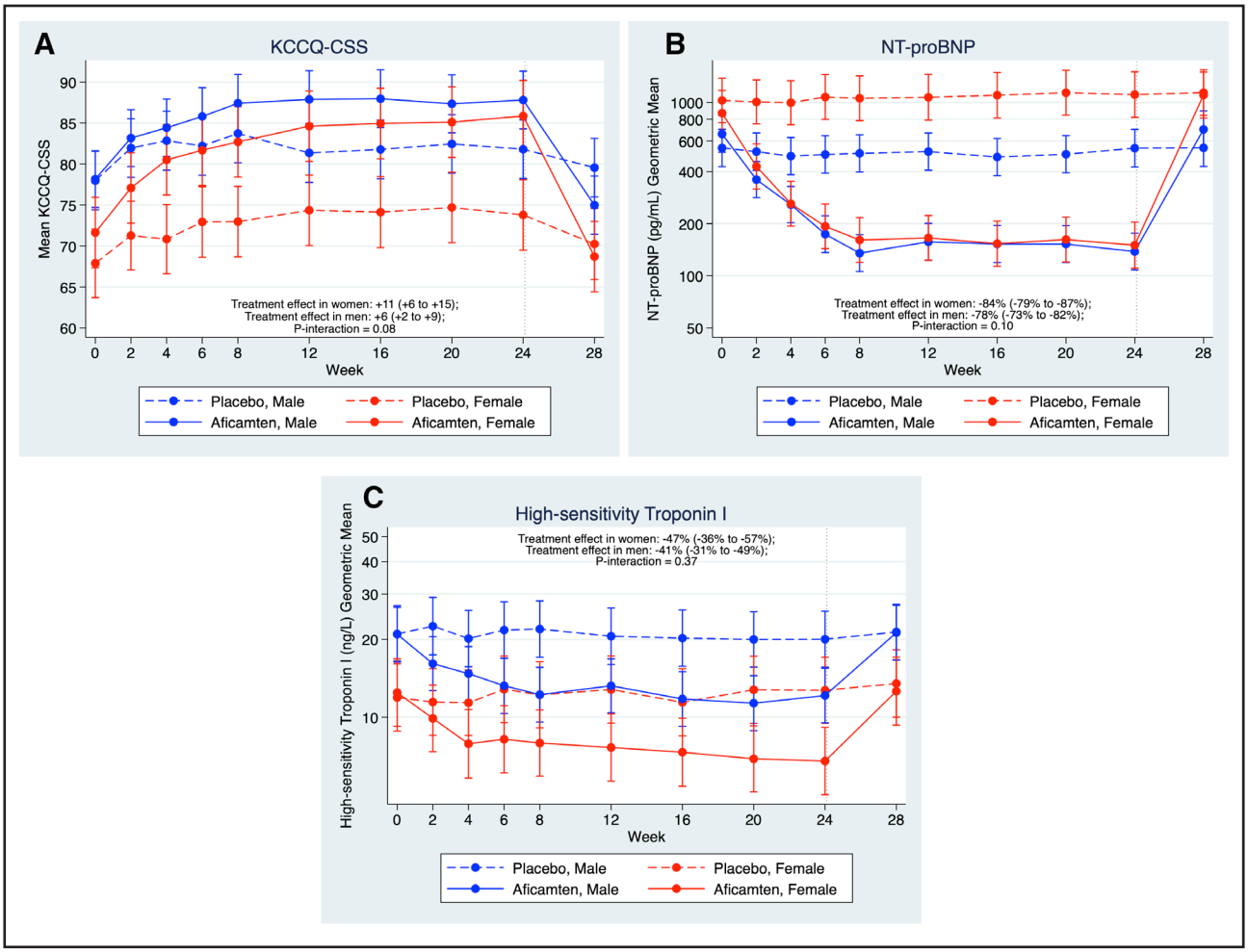


**Figure 1. Effect of aficamten on patient-reported health status, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and high-sensitivity troponin I over time.**

Effect of aficamten on Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS; **A**), NT-proBNP (**B**), and high-sensitivity troponin I over time in women (red) and men (blue) (**C**). $P_{interaction}$ values represent treatment-by-sex interaction at week 24, with baseline values, β-blocker use, and exercise modality as covariates. Weeks 24 to 28 represent the 4-week washout period.

## Adverse Events in Men and Women

Women and men had similar rates of serious adverse events (Table 4). Among women, those assigned to placebo had higher rates of serious adverse events compared with those assigned to aficamten. Rates of adverse events or serious adverse events leading to treatment interruption or discontinuation were low in both men and women (<2% for both sexes). While nominally more women developed LVEF <50% during the study (4.3% in women versus 0.6% in men), the treatment-by-sex interaction was not significant ($P_{interaction}$=1.00), indicating no treatment-related difference between sexes. Furthermore, there were no sex differences in the treatment effect of LVEF as a continuous variable (−4.4 [95% CI, −7.1 to −1.8] in women versus −4.9 [95% CI, −6.8 to −3.0] in men; Table 3; Figure 2). There were also no sex differences in adverse events of LVEF <40%, 45%, or 55% (Table S4). Rates of treatment-emergent heart failure were also low in both sexes (Table 4). There were no increased risks of aficamten-related serious adverse events or adverse events due to sex ($P_{interaction}$≥0.06). Women and men achieved similar doses of aficamten (Table S5).

## DISCUSSION

In this phase 3, international, randomized, double-blind trial in patients with symptomatic obstructive HCM, women were sicker, as characterized by higher NT-proBNP, lower baseline $pVO_2$, worse health status, higher NYHA functional class, and higher LVOT gradients at rest and with Valsalva. Women also had worse diastolic function at baseline. Despite these differences, women and men derived significant benefits from aficamten without higher risks of treatment-related adverse events. Treatment with aficamten also appeared to have a more favorable impact on echocardiographic measures of diastolic function in women compared with men though

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**Table 3. Treatment Effect of Aficamten on Echocardiographic Parameters in Men and Women**

| | N* | Women | Men | $P_{interaction}$† |
|---|---|---|---|---|
| LVOT gradients | | | | |
| LVOT gradient, rest, mm Hg | 271 | −45 (−54 to −35) | −36 (−43 to −28) | 0.13 |
| LVOT gradient, Valsalva, mm Hg | 271 | −56 (−67 to −44) | −46 (−54 to −38) | 0.13 |
| LV structure and systolic function | | | | |
| Maximal wall thickness, mm | 270 | −1.5 (−2.3 to −0.6) | −1.1 (−1.9 to −0.3) | 0.56 |
| Interventricular septum, mm | 268 | −1.4 (−2.3 to −0.4) | −0.8 (−1.6–0.1) | 0.39 |
| Inferior wall, mm | 259 | −0.9 (−1.8 to −0.0) | −0.7 (−1.4 to −0.1) | 0.72 |
| LV mass index, g/m² | 259 | −16.1 (−24.5 to −7.7) | −9.9 (−17.7 to −2.1) | 0.26 |
| LVEDVi, mL/m² | 267 | −0.1 (−2.0 to +1.8) | −0.3 (−2.3 to +1.6) | 0.87 |
| LVESVi, mL/m² | 267 | +1.4 (+0.4 to +2.4) | +1.8 (+0.9 to +2.8) | 0.57 |
| LVEF, % | 267 | −4.4 (−7.1 to −1.8) | −4.9 (−6.8 to −3.0) | 0.77 |
| GLS, % | 272 | −0.2 (−1.0 to +0.7) | −0.5 (−1.3 to +0.2) | 0.52 |
| LV diastolic function | | | | |
| LA volume index, mL/m² | 266 | −4.4 (−7.1 to −1.7) | −3.4 (−5.6 to −1.3) | 0.55 |
| LA width, mm | 257 | −2.7 (−4.2 to −1.1) | −2.5 (−4.0 to −1.1) | 0.84 |
| Peak E wave velocity, cm/s | 269 | −11.6 (−18.5 to −4.8) | −4.6 (−10.1 to +0.9) | 0.08 |
| Peak A wave velocity, cm/s | 265 | +0.4 (−5.9 to +6.7) | −4.3 (−9.3 to +0.8) | 0.26 |
| Lateral e' velocity, cm/s | 266 | +1.3 (+0.7 to +1.9) | +1.1 (+0.5 to +1.7) | 0.73 |
| Septal e' velocity, cm/s | 261 | +0.4 (−0.0 to +0.8) | +0.5 (+0.1 to +0.9) | 1.00 |
| Lateral E/e' | 264 | −5.4 (−7.2 to −3.5) | −2.8 (−4.1 to −1.5) | 0.013 |
| Septal E/e' | 260 | −4.5 (−6.7 to −2.3) | −2.9 (−4.2 to −1.6) | 0.13 |
| RV systolic function | | | | |
| TAPSE, mm | 245 | −2.7 (−4.2 to −1.1) | −1.6 (−3.0 to −0.2) | 0.32 |
| RV s' velocity, cm/s | 258 | −1.8 (−2.7 to −1.0) | −1.1 (−1.8 to −0.5) | 0.16 |

Treatment effect values represent mean change from baseline in aficamten relative to placebo adjusted for baseline values, β-blocker use, and exercise modality with 95% CI. GLS indicates global longitudinal strain; LA, left atrium; LAVi, left atrium volume index; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVOT, left ventricular outflow tract; RV, right ventricle; and TAPSE, tricuspid annular plane systolic excursion.

*N denotes the number of available data points in the statistical model to assess the effect of aficamten on echocardiographic parameters.

†$P_{interaction}$: treatment-by-sex interaction at week 24, with baseline values, β-blocker use, and exercise modality as covariates.

differences in baseline values may partially account for this finding.

HCM is one of the most common genetic disorders of the heart, and the prevalence of HCM appears to be similar in men and women.[1] However, women and men often present differently. Previous studies have shown that women were older and more symptomatic, and in some cohorts, women had worse outcomes such as progression to advanced heart failure and mortality, while others showed similar mortality.[5–7,10–12] Consistent with previous studies, women in our analysis were also older and had worse exercise baseline health status, higher NYHA functional class, and higher NT-proBNP levels. Studies have shown that women are more likely to have sarcomere-positive HCM[11,12]; however, there were no sex differences in the prevalence of known HCM-causing gene mutations in our cohort. Reassuringly, despite baseline clinical differences, the efficacy and safety profiles of aficamten were overall similar in men and women. While a higher number of women developed LVEF <50% during treatment, there was no treatment-by-sex interaction for this finding whether LVEF was assessed as a binary or continuous variable. The degree of LVEF decrease was similar in women (−4%) and men (−5%).

Previous studies have demonstrated that women with heart failure had worse health status compared with men.[13–16] Consistent with these studies, we found a lower baseline KCCQ-CSS in women compared with men. In a previous analysis of EXPLORER-HCM, mavacamten, a first-in-class cardiac myosin inhibitor, was found to result in a 14.8-point improvement of KCCQ-CSS in women and a 6.1-point improvement of KCCQ-CSS in men ($P_{interaction}$=0.0259).[7] In our analysis of SEQUOIA-HCM, compared with those receiving placebo, women treated with aficamten had an 11-point improvement in KCCQ-CSS, while men treated with aficamten had a 6-point improvement in KCCQ-CSS. The magnitudes of improvement were similar to those seen in EXPLORER, with an almost 2-fold improvement in KCCQ-CSS in women compared with men. While KCCQ-CSS is a prespecified secondary end point and the differences in improvement should be

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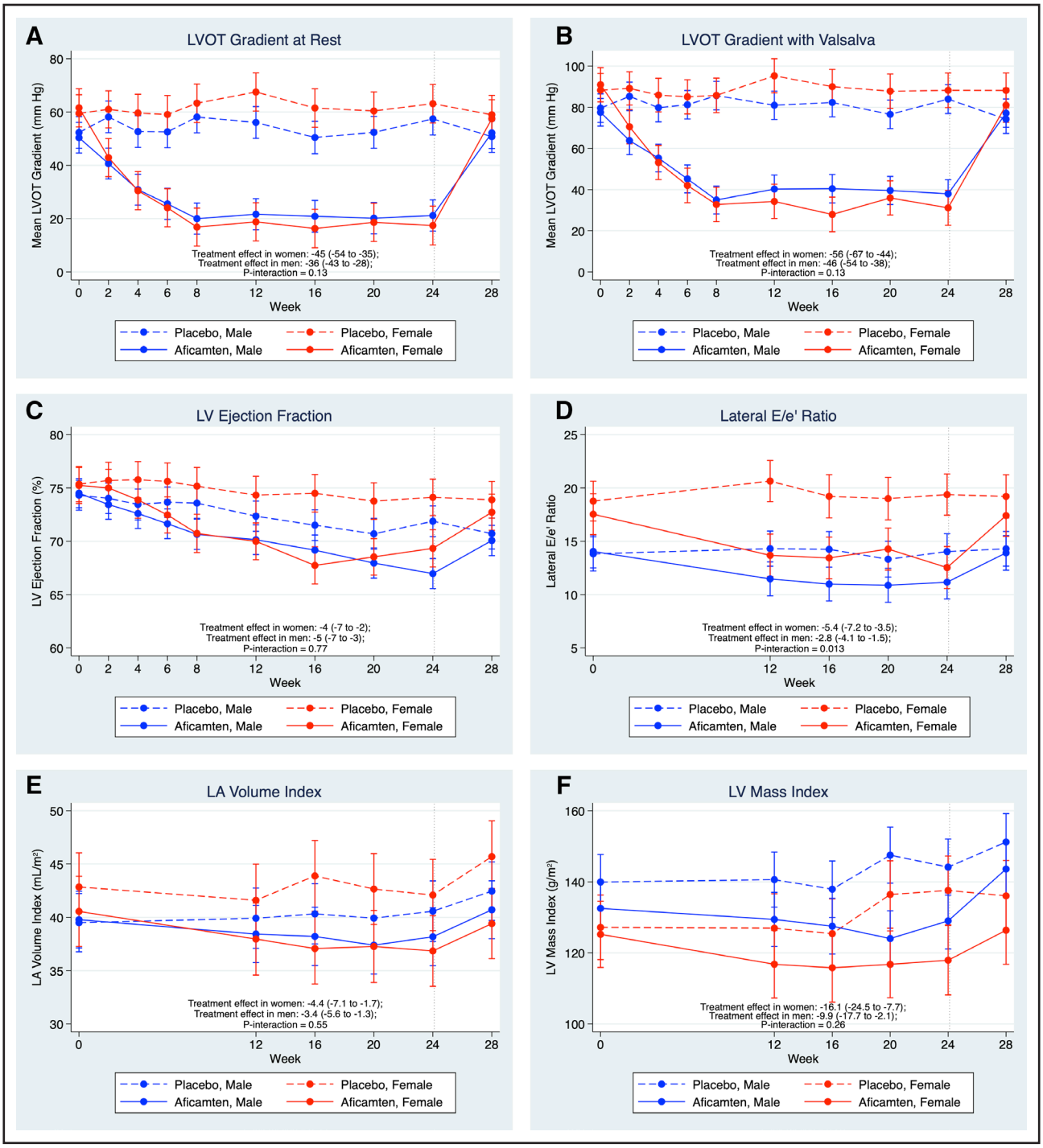


**Figure 2. Effect of aficamten on echocardiographic measures of cardiac structure and function over time.**
Effect of aficamten on left ventricular outflow tract (LVOT) gradient at rest (**A**), LVOT gradient with Valsalva (**B**), left ventricle (LV) ejection fraction (**C**), lateral E/e' ratio (**D**), left atrium (LA) volume index (**E**), and LV mass index over time in women (red) and men (blue) (**F**). Weeks 24 to 28 represent the 4-week washout period. $P_{interaction}$ values represent treatment-by-sex interaction at week 24, with baseline values, β-blocker use, and exercise modality as covariates.

considered as hypothesis-generating, these results are noteworthy and warrant further investigation as they have been demonstrated with both cardiac myosin inhibitors.

Our analysis also showed a higher baseline NT-proBNP in women compared with men, consistent with previous studies in patients with HCM,[7,17] as well as other populations of heart failure with preserved and reduced ejection fractions.[18] In EXPLORER-HCM, women had higher baseline NT-proBNP (mean level, 1704 ng/L) compared with men (mean level, 990 ng/L). Treatment with mavacamten resulted in a decrease in NT-proBNP in both sexes, with a 2-fold reduction in women

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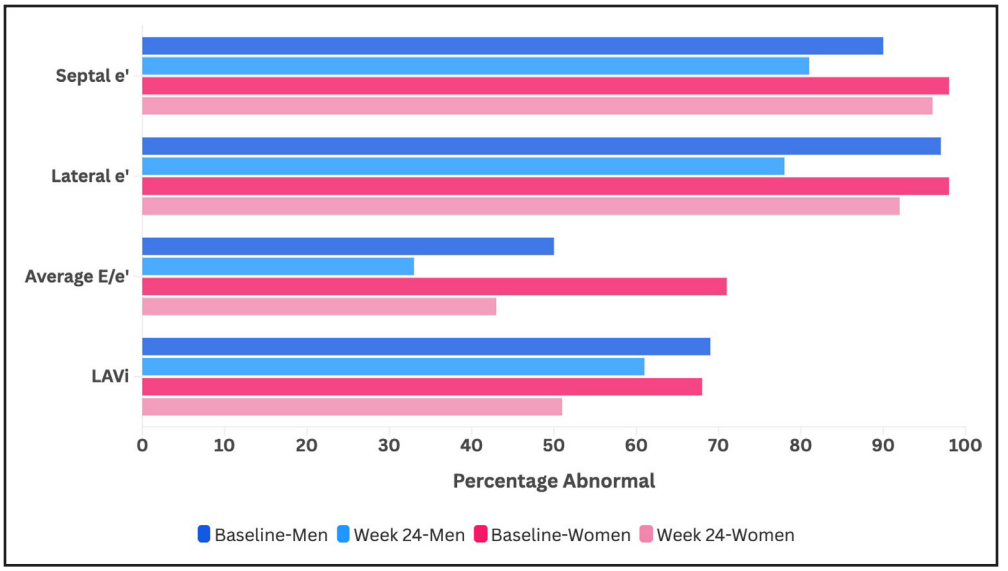


**Figure 3. Prevalence of abnormal left ventricular diastolic function measures and change over time in women and men treated with aficamten.**

Prevalence of abnormal left ventricular diastolic function measures in women (red) and men (blue) treated with aficamten at baseline and 24 weeks. LAVi indicates left atrium volume index. This figure was created with https://flourish.studio/.

compared with men (1322 ng/L in women compared with 649 ng/L in men).[7] In our analysis, women also had a higher absolute reduction in NT-proBNP levels (1214 mg/L in women versus 678 ng/mL in men), comparable to those observed in EXPLORER-HCM. When considering the higher NT-proBNP levels in women at baseline, the geometric mean proportional change in NT-proBNP was similar in men and women. NT-proBNP has important prognostic value,[19,20] and a decrease in NT-proBNP has been shown to accompany improvement in LVOT obstruction by both medical therapy and septal reduction.[9,21,22] In a previous analysis of echocardiographic measures in SEQUOIA-HCM, reduction in NT-proBNP was also associated with improvements in diastolic parameters, such as an increase in lateral and septal e' velocities and a decrease in lateral and septal E/e' ratios.

The differences in baseline cardiac structure and function in women and men are worth noting. Consistent with prior studies, our analysis noted a smaller LV chamber size and maximal LV wall thickness in women compared with men.[11] It has been well established that in healthy subjects, women have smaller heart chamber sizes, wall thickness, and LV mass, and such differences persist even after adjusting for height or body surface area.[23] Current guidelines use the same criteria of maximal LV wall thickness of 15 mm regardless of sex,[1,24] and this may reflect that women have more advanced phenotypes of HCM at the time of diagnosis, which may be contributing to a sicker profile (lower KCCQ-CSS, higher NT-proBNP levels, and higher NYHA class). Indeed, in addition to differences in LV chamber size, women also have lower lateral and septal e' velocities and higher E/e' ratios, suggesting that women

**Table 4. Adverse Events in Men and Women in SEQUOIA-HCM**

| | Women | | | Men | | | |
|---|---|---|---|---|---|---|---|
| | Overall (N=115) | Aficamten (n=56) | Placebo (n=59) | Overall (N=167) | Aficamten (n=86) | Placebo (n=81) | $P_{interaction}$* |
| Any SAE | 12 (10.4%) | 2 (3.6%) | 10 (16.9%) | 9 (5.4%) | 6 (7.0%) | 3 (3.7%) | 0.06 |
| Any SAE that led to the discontinuation of aficamten or placebo | 2 (1.7%) | 0 (0.0%) | 2 (3.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | NA |
| Any SAE that led to interruption of aficamten or placebo | 1 (0.9%) | 0 (0.0%) | 1 (1.7%) | 2 (1.2%) | 1 (1.2%) | 1 (1.2%) | NA |
| Any AE | 92 (80.0%) | 47 (83.9%) | 45 (76.3%) | 112 (67.1%) | 58 (67.4%) | 54 (66.7%) | 0.44 |
| Any AE that led to discontinuation of aficamten or placebo | 2 (1.7%) | 0 (0.0%) | 2 (3.4%) | 1 (0.6%) | 1 (1.2%) | 0 (0.0%) | NA |
| Any AE that led to interruption of aficamten or placebo | 2 (1.7%) | 1 (1.8%) | 1 (1.7%) | 2 (1.2%) | 1 (1.2%) | 1 (1.2%) | 1.00 |
| Core laboratory–reported LVEF <50% | 5 (4.3%) | 4 (7.1%) | 1 (1.7%) | 1 (0.6%) | 1 (1.2%) | 0 (0.0%) | 1.00 |
| Treatment-emergent cardiac failure | 2 (1.7%) | 2 (3.6%) | 0 (0.0%) | 1 (0.6%) | 1 (1.2%) | 0 (0.0%) | NA |

AE indicates adverse event; LVEF, left ventricular ejection fraction; SAE, serious adverse event; and SEQUOIA-HCM, Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM.

*$P_{interaction}$: treatment-by-sex interaction at week 24. Standard or exact logistic regression (for small event numbers) was used as appropriate.

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have worse diastolic function and higher LV filling pressures. These differences in diastolic measures could also contribute to worse health status and higher NT-proBNP in women. Reassuringly, both men and women demonstrated improvement in echocardiographic parameters of diastolic function with treatment of aficamten.

Other epidemiological cohorts have also demonstrated a higher LVOT gradient in women. For example, in 2123 patients (38% women) at Tufts HCM Institute, women were more likely to have peak resting LVOT gradient ≥30 mm Hg (45% in women versus 31% in men; $P<0.001$).[12] Similarly, among 5873 participants (38% women) in the Sarcomeric Human Cardiomyopathy Registry, women had a resting LVOT gradient of 35.5 mm Hg compared with 26.6 mm Hg in men ($P<0.001$).[10] Our patient population demonstrated similar sex differences in resting LVOT gradients. The higher LVOT gradients could reflect women being sicker at diagnosis or a reflection of differences in cardiac structure. For example, a smaller LV chamber size, in particular a small end diastolic volume, may lead to more obstruction. In the Sarcomeric Human Cardiomyopathy Registry, sex differences in LVOT obstruction did not persist after adjusting for LV end-diastolic volume.[10] Treatment with aficamten appears to result in a greater reduction in LVOT gradients in women compared with men at 12 weeks; however, this did not persist after 24 weeks. Additional analysis of FOREST-HCM (Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Aficamten in Adults With HCM; Unique identifier: NCT048485060), an ongoing open-label extension study for patients with HCM who completed a parent study of aficamten, may help elucidate whether there are sex differences in aficamten-related reduction in LVOT gradients at longer follow-up.

While it is expected that the prevalence of HCM may be similar in men and women, prior studies have noted a slight male predominance. For example, in 1 study of 969 consecutive patients at 3 institutions in Italy, Minnesota, and Massachusetts, there was a 3:2 male predominance.[5] This mirrors our trial population in SEQUOA-HCM (40.8% women), EXPLORER-HCM (40.6% women),[7] the Sarcomeric Human Cardiomyopathy Registry (37.9% women),[10] and the Tufts HCM Institute cohort (37.4%).[12] In addition, there are notable differences in the clinical presentation of HCM in men and women; for example, women are often diagnosed at an older age and are more likely to present with pathological sarcomeric mutations.[10] It is unclear whether this reflects an underdiagnosis of women or a true biological basis of higher prevalence in men. Further efforts are needed to ensure adequate representation of women in clinical trials.

These results should be considered in the context of several limitations. First, our analysis was a prespecified subgroup analysis of a randomized clinical trial, and results should be considered in the context of specific trial inclusion and exclusion criteria. The small number in each subgroup may have limited our power to detect certain differences. Second, the majority of participants in SEQUOIA-HCM were White (79%) or Asian (19%), further limiting the generalizability of our findings to other races and ethnicities. Third, the treatment duration of SEQUOIA-HCM was 24 weeks, thus limiting our ability to assess long-term outcomes; FOREST-HCM will provide further insights on sex differences in long-term outcomes.

## CONCLUSIONS

Women in SEQUOIA-HCM tended to have greater disease burden, as characterized by worse health status, higher NT-proBNP levels, higher LVOT gradients, and more severe diastolic dysfunction. Despite these differences, women and men derived similar improvements in exercise capacity and secondary end points. These results demonstrate a similar benefit of aficamten treatment in men and women.

## ARTICLE INFORMATION

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### Disclosures

The institution of Dr Wang received fees for core laboratory services from Alexion, Cytokinetics, and Bristol Myers Squibb (BMS), received a travel grant from Cytokinetics, and has individual stocks in Pfizer and Gilead Sciences. Dr Pabon received travel support from Bayer. Dr Barriales-Villa received consultant/advisor fees from MyoKardia/BMS. Dr Claggett received personal consulting fees from Alnylam, BMS, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, and Rocket and

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has served on a data and safety monitoring board for Novo Nordisk. Dr Coats received research grants from Roche Diagnostics, speaker fees from Alnylam and Pfizer, and consulting fees from Cytokinetics Inc, Bayer, Sanofi (paid to herself), and Roche Diagnostics (paid to herself and her institution) and is the co-chair of the Hypertrophic Cardiomyopathy Committee for European Society of Cardiology Heart Failure Association (unpaid). Dr Maron received consultant/advisor fees from Imbria and Edgewise and steering committee fees for SEQUOIA-HCM (Safety, Efficacy and Quantitative Understanding of Obstruction Impact of Aficamten in HCM) from Cytokinetics Inc. Dr Masri received research grants from Pfizer, Ionis, Attralus, Cytokinetics Inc, and Janssen; consultant/advisor fees from Cytokinetics Inc, BMS, BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Akros, Edgewise, Rocket, Lexeo, Prothena, BioMarin, AstraZeneca, Avidity, Neurimmune, and Tenaya; and steering committee fees for SEQUOIA-HCM from Cytokinetics Inc. Dr Meder received speaker and advisory honoraria from Cytokinetics and BMS. Dr Nassif received research and grant support from AstraZeneca and Cytokinetics Inc and consulting/advisory fees from Vifor and Cytokinetics Inc. Dr Olivotto received speakers' bureau fees from Boston Scientific, Amicus, and Novartis; consultant/advisor fees from BMS, Cytokinetics Inc, Sanofi Genzyme, Amicus, Bayer, Tenaya, and Rocket Pharma; and research grant funding from BMS, Cytokinetics Inc, Sanofi Genzyme, Amicus, Bayer, Menarini International, and Boston Scientific. Dr Owens is a consultant for Alexion, Avidity, Bayer, BMS, Cytokinetics, Biomarin, Edgewise, Imbria, Lexeo, Corvista, Tenaya, Stealth, and Bridgebio and receives a research grant to the institution from BMS. Dr Saberi receives consulting honoraria from BMS and Cytokinetics and institutional research grants from BMS, Cytokinetics, Lexicon, and Edgewise. Drs Jacoby, Heitner, Kupfer, and Malik and A. Wohltman are employees and shareholders of Cytokinetics Inc and received advisory board fees from Cytokinetics. Dr Solomon received grants from Actelion, Amgen, Bellerophon, BMS, Cytokinetics, Alnylam, AstraZeneca, Bayer, Celladon, and Eidos and received consultant/adviser fees from Abbott, Akros, Amgen, AstraZeneca, Boehringer Ingelheim, Cardior, Corvia, Daiichi Sankyo, Lilly, MyoKardia, Roche, Quantum Genomics, Janssen, Tenaya, Dinagor, CellProThera, American Regent, Lexicon, Akros, Action, Alnylam, Arena, Bayer, BMS, Cardurion, Cytokinetics, GlaxoSmithKline, Merck, Novartis, Theracos, Cardurion, Cardiac Dimensions, Sanofi-Pasteur, Tremeau, Modera, Sarepta, Anacardio, and Puretech Health. Dr Hegde received advisory board fees from Cytokinetics. The institution of Dr Hegde received fees for core laboratory services from Cytokinetics and BMS. The other authors report no conflicts.

## Supplemental Material

Tables S1–S5

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