SEQUOIA HCM

Scientific Sessions

Effect Of Aficamten in Women Compared with Men with Obstructive Hypertrophic Cardiomyopathy in SEQUOIA-HCM

Xiaowen Wang, MD, MPH

Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

On behalf of Maria A. Pabon, Tracy T. Makuvire, Reziwanguli Maimaiti, Theodore P. Abraham, Roberto Barriales-Villa, Brian L. Claggett, Caroline J. Coats, Martin S. Maron, Ahmad Masri, Benjamin Meder, Michael E. Nassif, Iacopo Olivotto, Anjali T. Owens, Sara Saberi, Daniel L. Jacoby, Stephen B. Heitner, Stuart Kupfer, Fady I. Malik, Amy Wohltman, Scott D. Solomon, Sheila M. Hegde

American Heart Association.

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BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

@wendywangmd

xwang15@mgb.org

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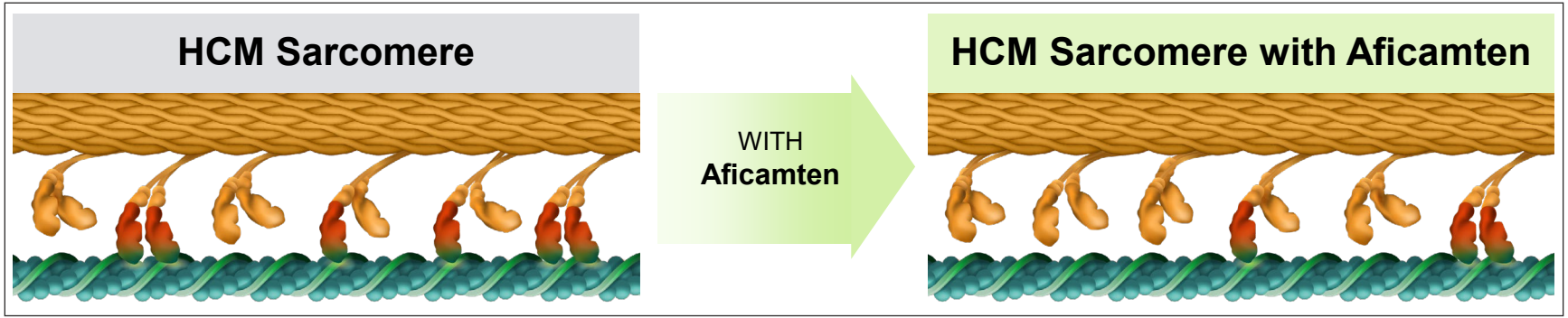
DISCLOSURES

Xiaowen Wang, MD, MPH: institution received fees for core lab services from Alexion, Cytokinetics and Bristol Myers Squibb, has received travel grant from Cytokinetics, and has individual stocks in Pfizer and Gilead Sciences.

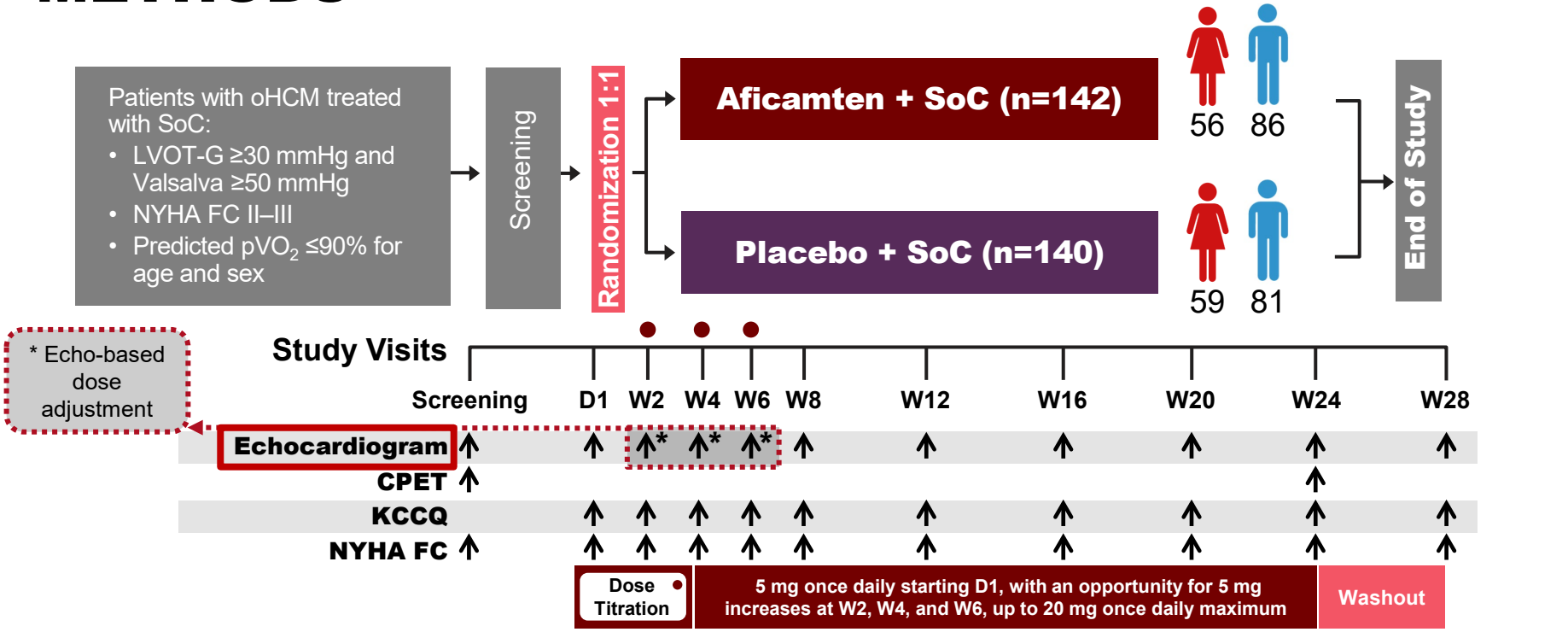
The SEQUOIA-HCM trial is funded by Cytokinetics, Incorporated.

BACKGROUND

- Aficamten is a next-in-class cardiac myosin inhibitor, a small-molecule selective inhibitor of the cardiac myosin ATPase, which reduces contractility by reversibly binding to cardiac myosin and reducing excessive myosin-actin cross-bridges.
- In SEQUOIA-HCM, aficamten improved exercise capacity (pVO_2) and lowered resting and Valsalva LVOT gradients in adults with symptomatic obstructive HCM (oHCM).



METHODS



Echocardiographic measurements were performed by a core imaging laboratory.

Primary end point: change in peak oxygen uptake by cardiopulmonary exercise test at 24 weeks.

Baseline Clinical Characteristics

	Women (N = 115)	Men (N = 167)	P-value
Age	64 ± 11	56 ± 13	<0.001
Background HCM therapy			
Beta 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, Watts	97 ± 35	140 ± 35	<0.001
% of Predicted Oxygen Uptake	56.9 ± 11.9	56.8 ± 11.9	0.93
pVO_2, mL/kg/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

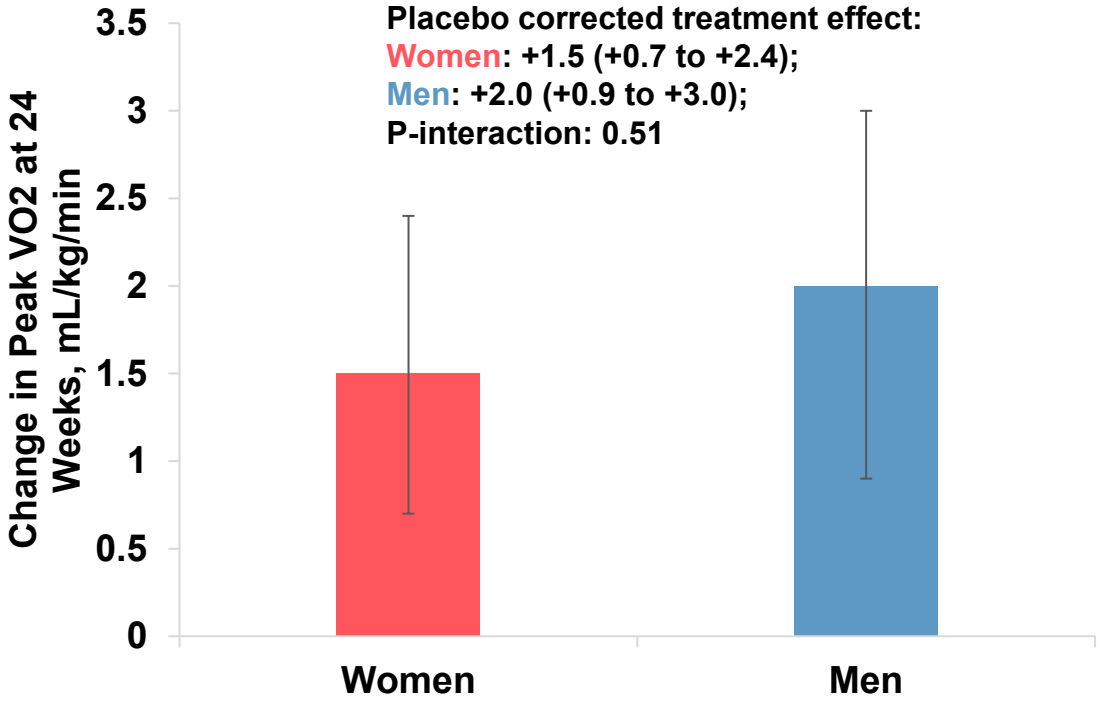
KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; pVO_2: peak oxygen uptake.

Baseline Echocardiographic Characteristics

	Women (N = 115)	Men (N = 167)	P-value
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
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/m^2	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/m^2	41.7 ± 15.3	39.6 ± 12.8	0.22
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
Lateral e' velocity, cm/s	5.4 ± 1.9	6.5 ± 2.2	<0.001
Lateral E/e'	18.2 ± 8.5	13.9 ± 6.3	<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

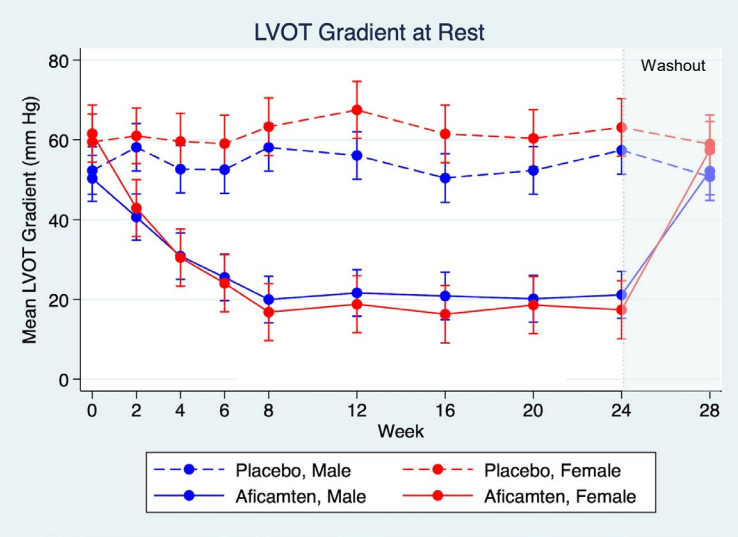
GLS = global longitudinal strain; LA: left atrium; LV: left ventricular; LVEDVi: LV end-diastolic volume index; LVEF: LV ejection fraction; LVESVi: LV end-systolic volume index; LVOT: LV outflow tract; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion.

Effect of Aficamten on Primary End Point

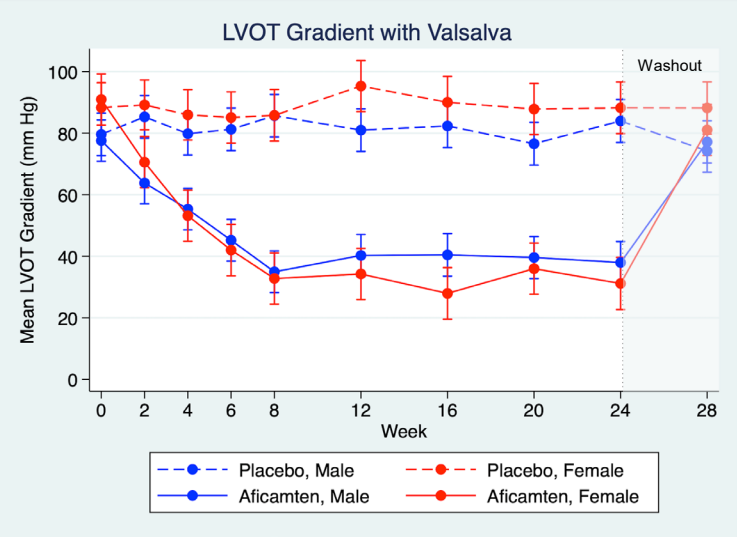


Treatment effects and P-interactions included baseline values, beta-blocker use and exercise modality as covariates
P-interactions represent treatment-by-sex interaction at week 24.

Effect of Aficamten on LVOT Gradients



Women: -45 (-54 to -35) mm Hg;
Men: -36 (-43 to -28) mm Hg;
P-interaction: 0.13

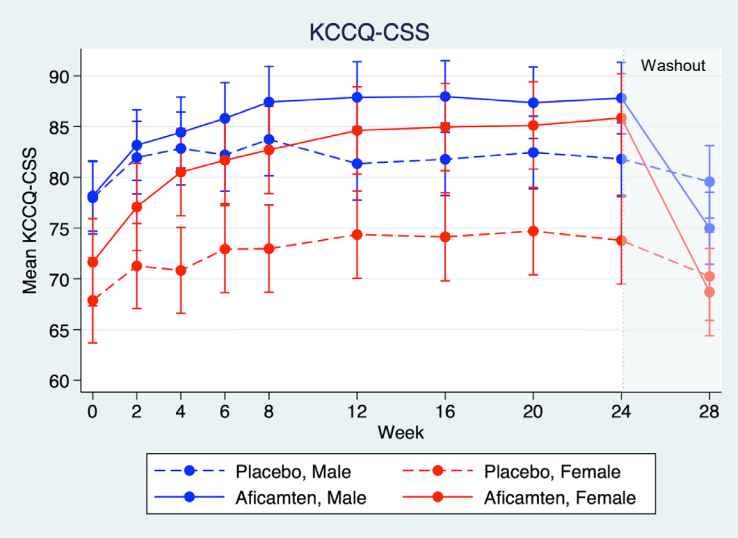


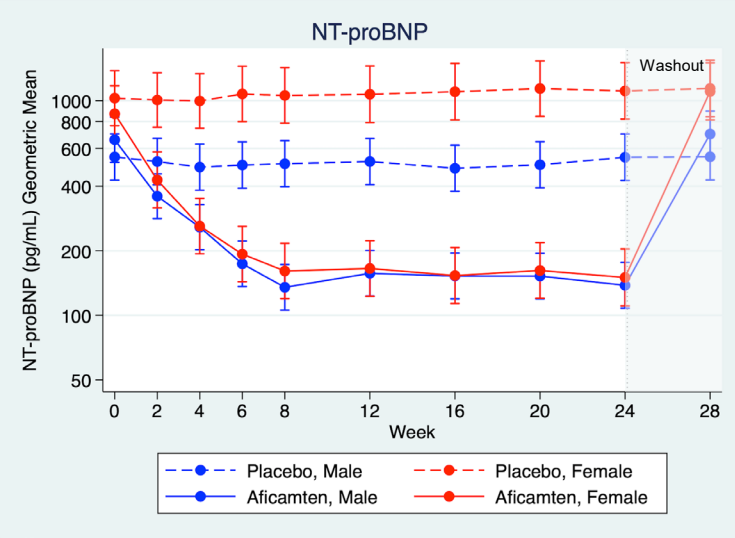
Women: -56 (-67 to -44) mm Hg;
Men: -46 (-54 to -38) mm Hg;
P-interaction: 0.13

Effect of aficamten on LVOT gradients at rest and with Valsalva over time in women (red) and men (blue).
Treatment effects and P-interactions included baseline values, beta-blocker use and exercise modality as covariates.
P-interactions represent treatment-by-sex interaction at week 24.

LVOT = left ventricular outflow tract

Effect of Aficamten on health status and NT-proBNP





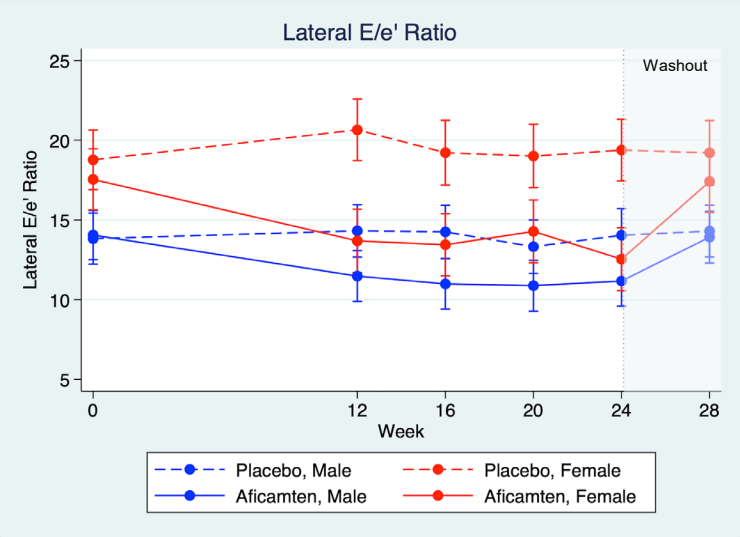
Women: +11 (+6 to +15);
Men: +6 (+2 to +9);
P-interaction: 0.08

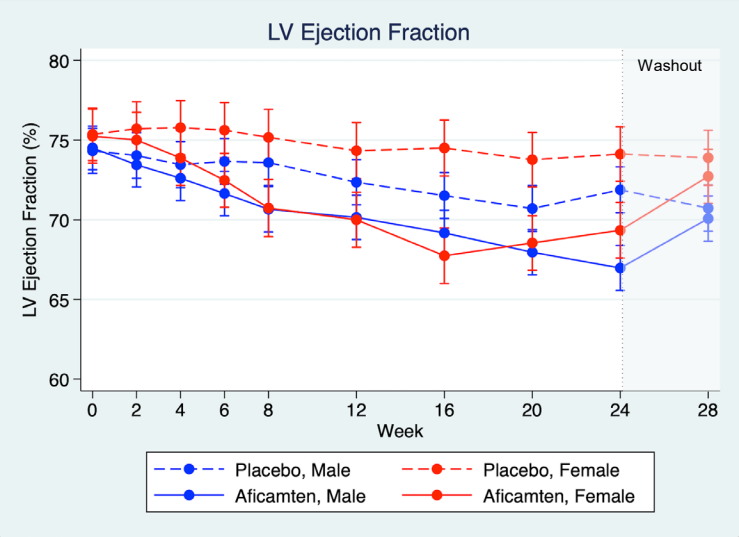
Women: -84% (-79% to -87%);
Men: -78% (-73% to -82%);
P-interaction: 0.10

Effect of aficamten on KCCQ-CSS and NT-proBNP levels over time in women (red) and men (blue).
Treatment effects and P-interactions included baseline values, beta-blocker use and exercise modality as covariates
P-interactions represent treatment-by-sex interaction at week 24.

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Effect of Aficamten on E/e' ratio and LV ejection fraction





Women: -5.4 (-7.2 to -3.5);
Men: -2.8 (-4.1 to -1.5);
P-interaction: 0.013

Women: -4% (-7% to -2%);
Men: -5% (-7% to -3%);
P-interaction: 0.77

Effect of aficamten on LV ejection fraction and lateral E/e' ratio over time in women (red) and men (blue).
Treatment effects and P-interactions included baseline values, beta-blocker use and exercise modality as covariates.
P-interactions represent treatment-by-sex interaction at week 24.

LV = left ventricle

Conclusion

- 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 demonstrated similar benefits of aficamten in women and men with symptomatic oHCM.

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- Investigators and study site staff
- Data Monitoring Committee members
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Circulation: Heart Failure

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@wendywangmd xwang15@mgb.org

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