Aficamten for the Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy

SEQUOIA-HCM, an international multicenter Phase 3 trial

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the SEQUOIA-HCM Investigators

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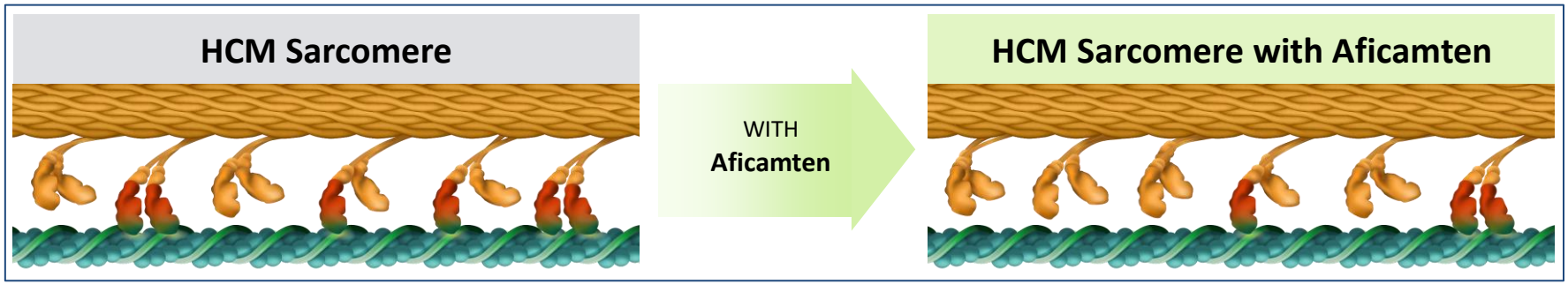
Heart Failure & World Congress on Acute Heart Failure 2024

Background

- Left ventricular outflow tract obstruction in HCM often leads to limiting symptoms: exertional dyspnea and reduced exercise capacity
- Hypercontractility is an important disease-related mechanism responsible for outflow tract obstruction
- Current first-line medical therapies for oHCM have limited efficacy and important side effects
- Aficamten is an investigational, novel oral selective cardiac myosin inhibitor, which reduces LV contractility and is designed for an optimal pharmacodynamic profile[1]

1. Chuang C, et al. *J Med Chem* 2021;64(19): 14142-14152.

Aficamten – Mechanism and Key Pharmacologic Features



- **Once daily dosing with half-life → 3.4 days**
  - Steady state achieved by 2 weeks, allowing rapid dose adjustments
  - Rapid reversibility
- **Shallow dose–response relationship (wide therapeutic window)**
  - Small changes in LVEF as aficamten dose is increased
  - No need for serum plasma drug concentration monitoring
- **Minimal drug-drug interactions** → No clinically significant CYP inhibition or induction

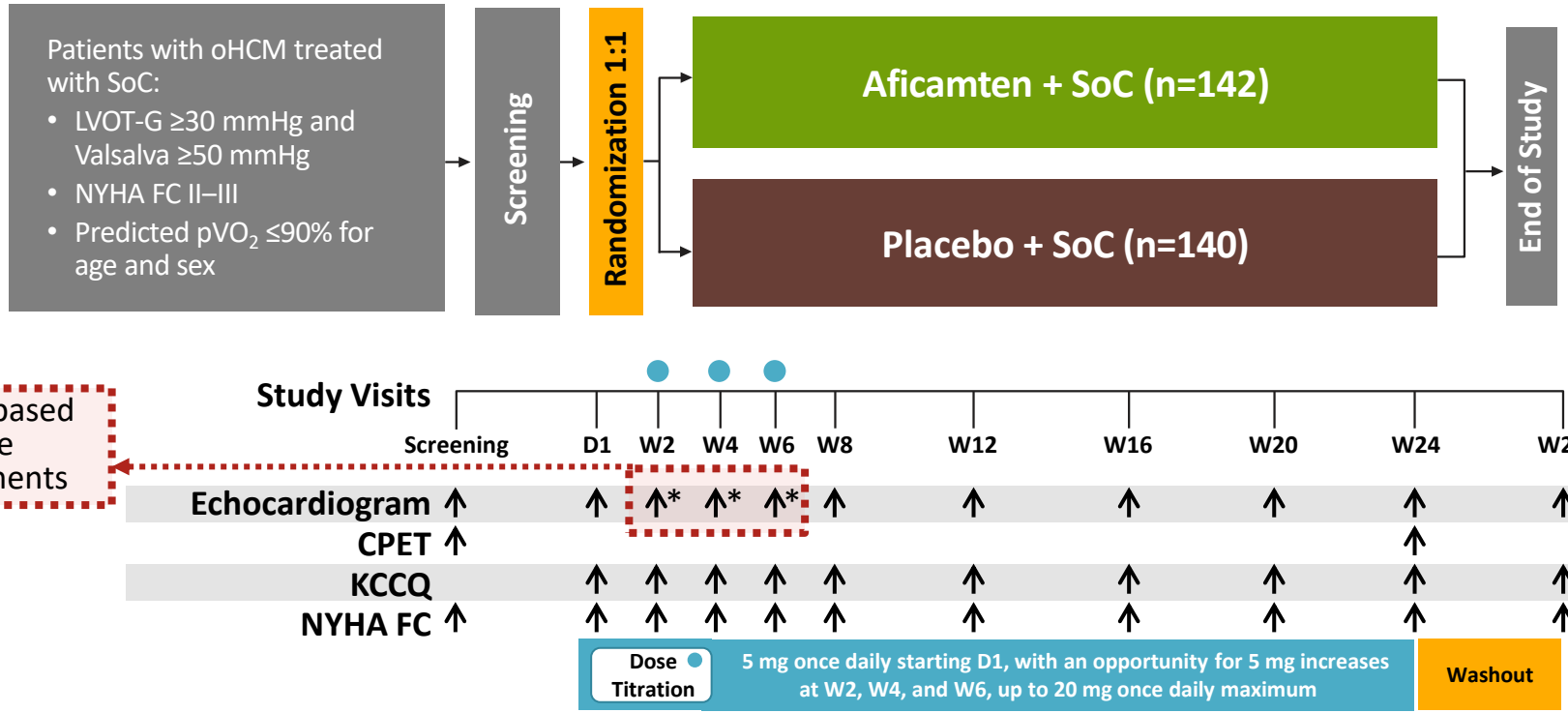
Aficamten – Mechanism and Key Pharmacologic Features

In the REDWOOD-HCM Phase 2 study, aficamten was shown to safely and significantly decrease outflow tract gradients by mitigating cardiac hypercontractility[1]

Leading to Phase 3 SEQUOIA-HCM…

1. Maron MS, et al. *J Am Coll Cardiol* 2023;81:34-45.

SEQUOIA-HCM – Study Design



CPET, cardiopulmonary exercise testing; D, day; IP, investigational product; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT-G, left ventricular outflow tract obstruction gradient; NYHA FC, New York Heart Association functional class; SoC, standard of care; W, week.

Coats CJ, et al. *J Am Coll Cardiol HF* 2024;12:199–215.

Endpoints – Hierarchical Analysis

Primary Endpoint:

- **Change in peak oxygen uptake (pVO_2) by CPET from baseline to Week 24**

Secondary Endpoints: **If *P*<0.05, then go to next step**

1. Change in KCCQ-CSS from baseline to Week 24
2. Proportion of patients with ≥1 class improvement in NYHA FC from baseline to Week 24
3. Change in post-Valsalva LVOT-G from baseline to Week 24
4. Proportion of patients with post-Valsalva LVOT-G <30 mmHg at Week 24
5. Duration of eligibility for SRT during the 24-week treatment period in patients who were eligible for SRT at baseline
6. Change in KCCQ-CSS from baseline to Week 12
7. Proportion of patients with ≥1 class improvement in NYHA FC from baseline to Week 12
8. Change in post-Valsalva LVOT-G from baseline to Week 12
9. Proportion of patients with post-Valsalva LVOT-G <30 mmHg at Week 12
10. Change in total workload during CPET from baseline to Week 24

FC, functional class; SRT, septal reduction therapy.

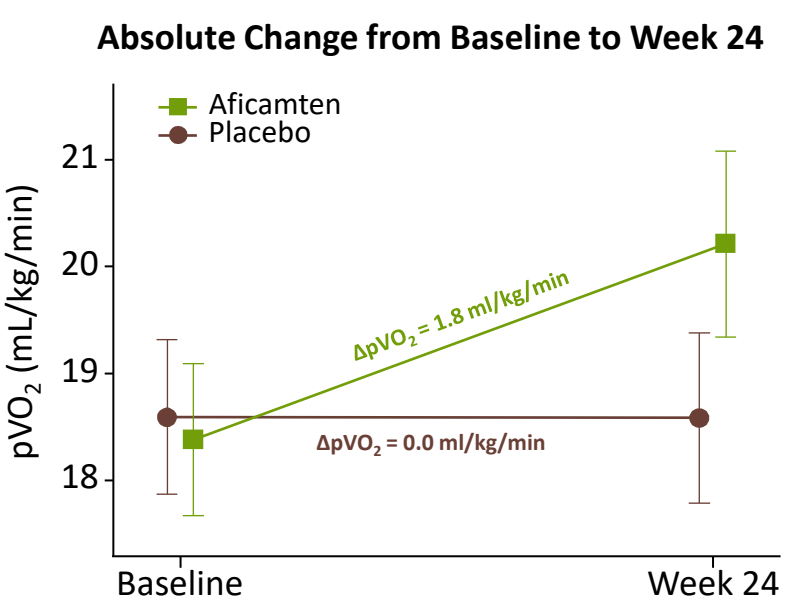
Baseline Characteristics

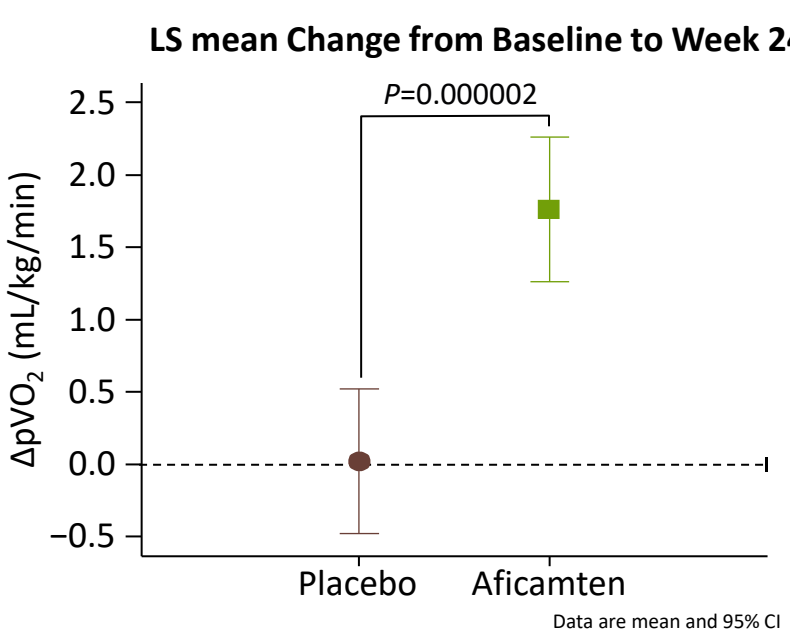
	Aficamten n=142	Placebo n=140
Age, y	59.2 ± 12.6	59.0 ± 13.4
Female sex, n (%)	56 (39.4)	59 (42.1)
Race, n (%)		
White	108 (76.1)	115 (82.1)
Geographic region, n (%)		
North America	49 (34.5)	45 (32.1)
China	24 (16.9)	22 (15.7)
Europe and Israel	69 (48.6)	73 (52.1)
Medical history, n (%)		
Hypertension	75 (52.8)	70 (50.0)
Paroxysmal atrial fibrillation	21 (14.8)	20 (14.3)
Permanent atrial fibrillation	2 (1.4)	1 (0.7)
CPET		
pVO_2 (mL/kg/min)	18.5 (4.5)	18.6 (4.5)
Percent of predicted pVO_2 (%)	58 (13)	57 (12)

	Aficamten n=142	Placebo n=140
Background HCM therapy, n (%)		
Beta-blocker	86 (60.6)	87 (62.1)
Calcium channel blocker	45 (31.7)	36 (25.7)
Disopyramide	16 (11.3)	20 (14.3)
None	19 (13.4)	22 (15.7)
KCCQ-CSS	76 ± 18	74 ± 18
NYHA FC, n (%)		
II	108 (76.1)	106 (75.7)
III/IV	34 (23.9)	34 (24.3)
Median NT-proBNP (IQR), pg/mL	818 (377–1630)	692 (335–1795)
Median hs-cTnI (IQR), ng/L	12.9 (7.6–33.6)	11.5 (7.7–25.0)
Echocardiographic parameters		
Valsalva LVOT-G, mmHg	82.9 ± 32	83.3 ± 33
Resting LVOT-G, mmHg	54.8 ± 27	55.3 ± 32
LVEF, %	74.8 ± 5.5	74.8 ± 6.3
Maximal LV wall thickness, mm	20.7 ± 3.0	21.0 ± 3.0

Values are the mean ± SD unless otherwise indicated.

Primary Endpoint – Change in pVO_2

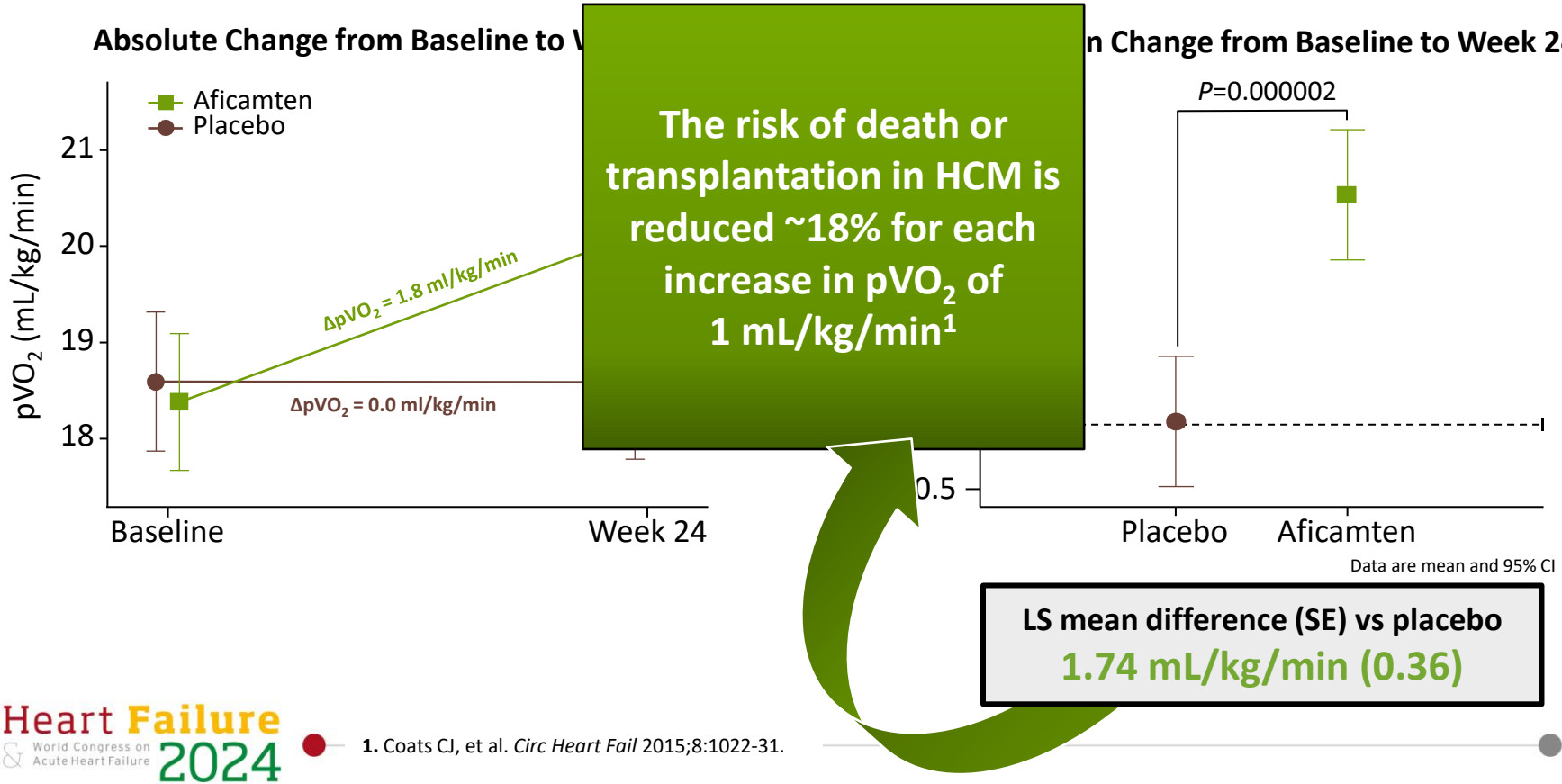




Data are mean and 95% CI

LS mean difference (SE) vs placebo
1.74 mL/kg/min (0.36)

Primary Endpoint – Change in pVO_2



1. Coats CJ, et al. *Circ Heart Fail* 2015;8:1022-31.

Subgroup Analyses – Change in pVO_2

	n (Afi/Plb)	Aficamten LS mean	Placebo LS mean	Mean difference (95% CI)
Age				
<65 y	85/84	2.4	0.4	2.0 (1.1, 2.8)
≥65 y	57/56	0.9	−0.5	1.4 (0.3, 2.5)
Sex				
Male	86/81	2.5	0.7	1.8 (0.9, 2.7)
Female	56/59	0.6	−0.8	1.4 (0.4, 2.5)
Baseline BMI				
<30 kg/m^2	97/94	1.9	0.1	1.8 (1.0, 2.7)
≥30 kg/m^2	45/46	1.4	−0.2	1.6 (0.3, 2.8)
Baseline Median LVEF				
≤75.6%	73/68	1.9	0.0	1.8 (0.8, 2.8)
>75.6%	69/72	1.7	0.0	1.6 (0.6, 2.6)
Baseline NYHA FC				
Class II	108/106	2.0	0.3	1.7 (0.9, 2.5)
Class III /IV	34/34	1.0	−0.9	1.9 (0.5, 3.3)
Baseline Median KCCQ-CSS				
≤78.1	67/75	1.7	−0.1	1.8 (0.8, 2.8)
>78.1	75/65	1.8	0.1	1.7 (0.7, 2.6)
Baseline Median NT-proBNP				
≤ 788 pg/mL	66/73	2.2	0.6	1.7 (0.7, 2.7)
> 788 pg/mL	73/65	1.4	−0.6	2.0 (1.0, 2.9)
CPET Modality				
Treadmill	78/77	2.5	0.2	2.3 (1.4, 3.2)
Bicycle	64/63	0.9	−0.1	1.0 (−0.0, 2.1)
Baseline Median pVO_2				
≤18.4 mL/kg/min	74/67	1.5	−0.1	1.6 (0.6, 2.5)
>18.4 mL/kg/min	68/73	2.0	0.1	1.9 (1.0, 2.9)
Baseline Beta-Blocker Use				
Yes	86/87	1.4	−0.2	1.6 (0.7, 2.5)
No	56/53	2.2	0.2	1.9 (0.8, 3.1)
Baseline Median Resting LVOT				
≤51.1 mmHg	72/69	1.8	0.5	1.3 (0.3, 2.3)
>51.1 mmHg	70/71	1.7	−0.4	2.1 (1.2, 3.1)
Genotype				
Positive	20/22	1.6	−1.0	2.6 (0.9, 4.2)
Negative	71/70	1.4	−0.1	1.4 (0.5, 2.3)

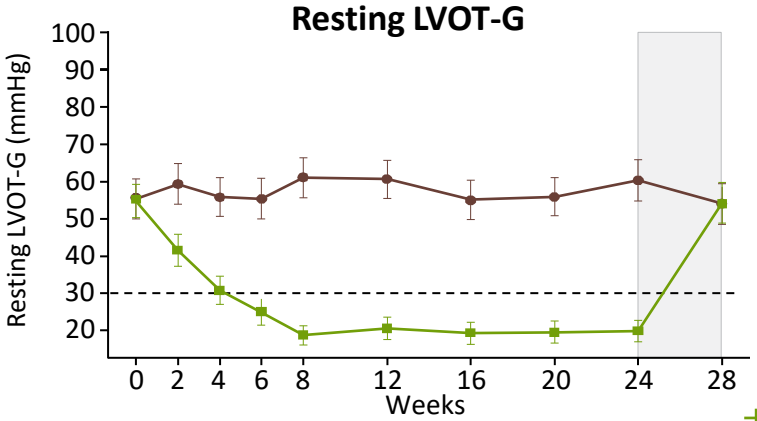
Interaction *P* values were >0.05 for all prespecified subgroups

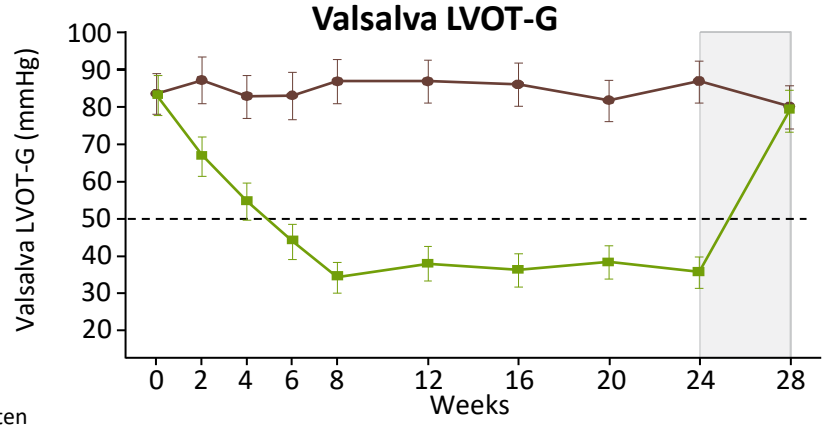
BMI, body mass index; CPET, cardiopulmonary exercise test; KCCQ-CCS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; LS, least squares; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA FC, New York Heart Association functional class; pVO_2, peak oxygen uptake.

Overview of All Prespecified Endpoints

Endpoints	*P* value
Primary Endpoint	
pVO_2 change from baseline to Week 24	**<0.0001**
Secondary Endpoints	
1. KCCQ-CSS change from baseline to Week 24	**<0.0001**
2. % NYHA class improvement by at least 1 class at Week 24	**<0.0001**
3. Valsalva LVOT-G change from baseline to Week 24	**<0.0001**
4. % Valsalva LVOT-G <30 mmHg at Week 24	**<0.0001**
5. Duration of SRT-eligible during 24 weeks of treatment	**<0.0001**
6. KCCQ-CSS change from baseline to Week 12	**<0.0001**
7. % NYHA class improvement by at least 1 class at Week 12	**<0.0001**
8. Valsalva LVOT-G change from baseline to Week 12	**<0.0001**
9. % Valsalva LVOT-G <30 mmHg at Week 12	**<0.0001**
10. Total workload change from baseline to Week 24	**<0.0001**

Secondary and Exploratory Endpoints

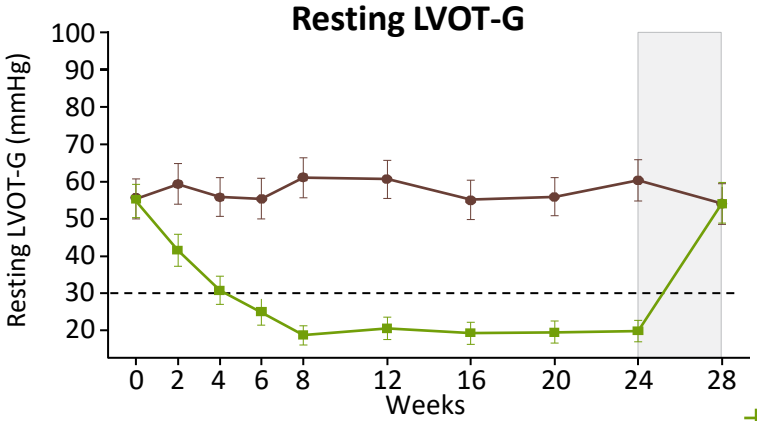


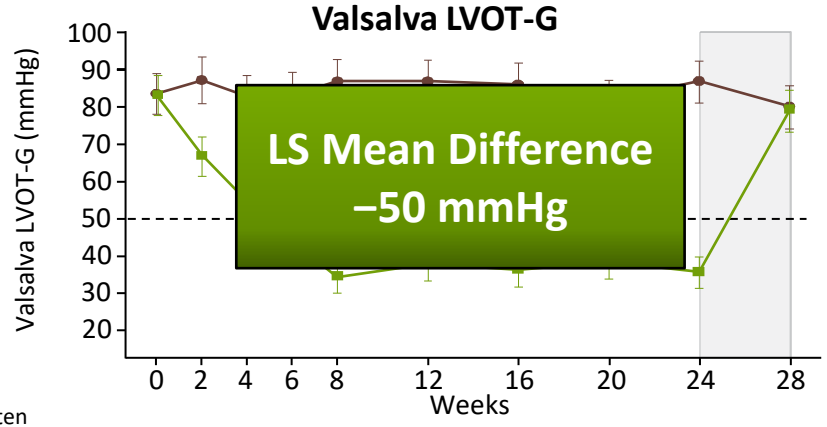


Aficamten
Placebo
Washout

Error bars are 95% CI

Secondary and Exploratory Endpoints





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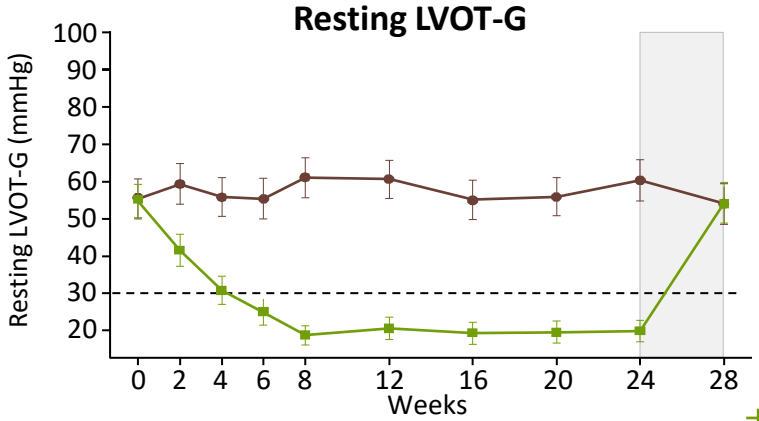

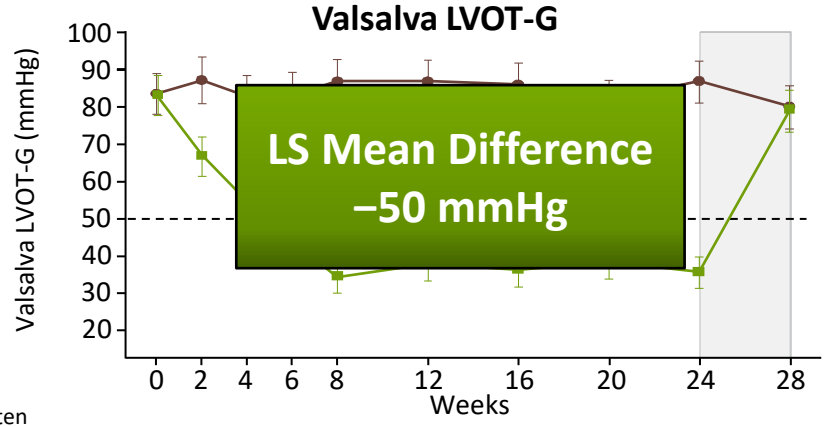

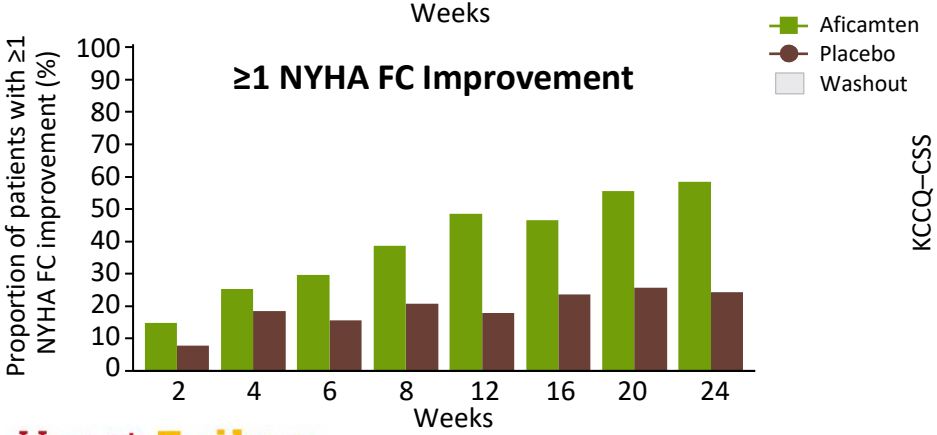

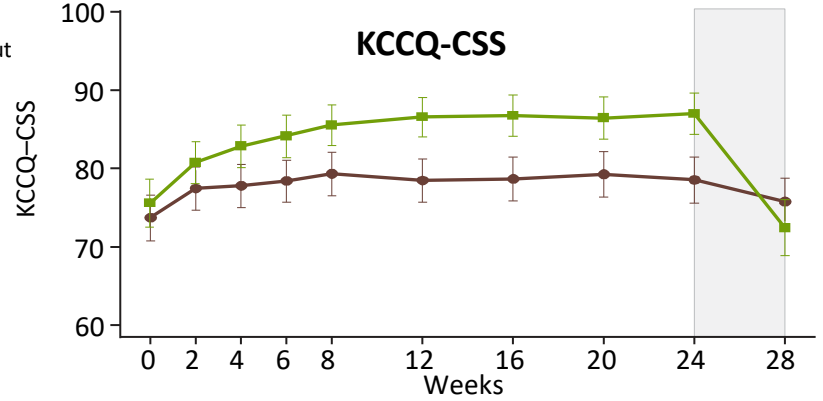

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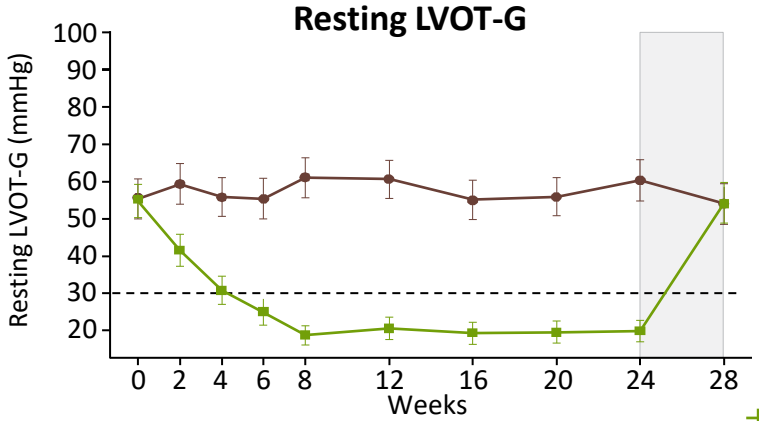

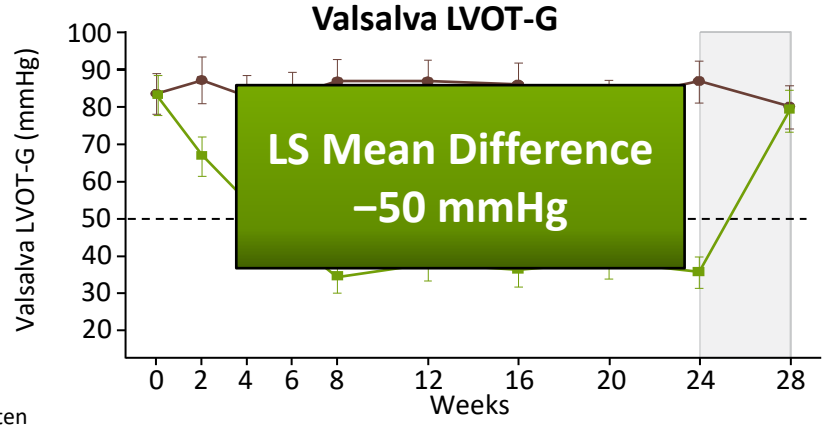

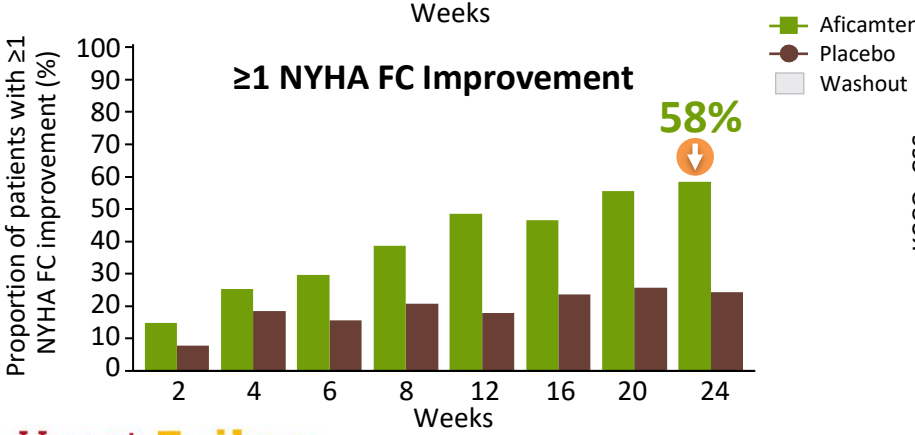

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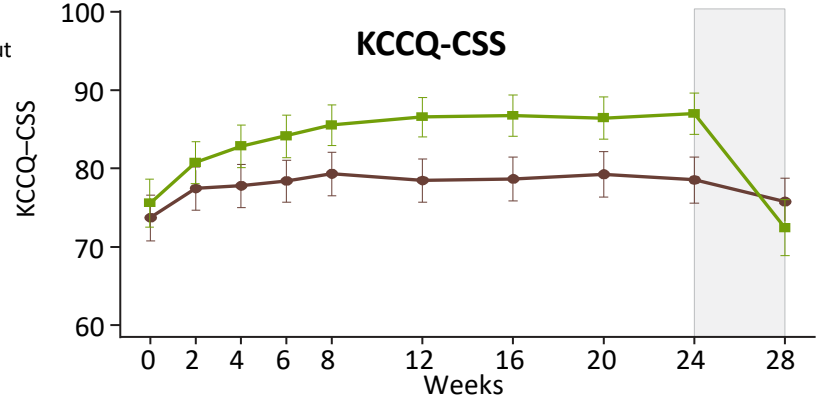

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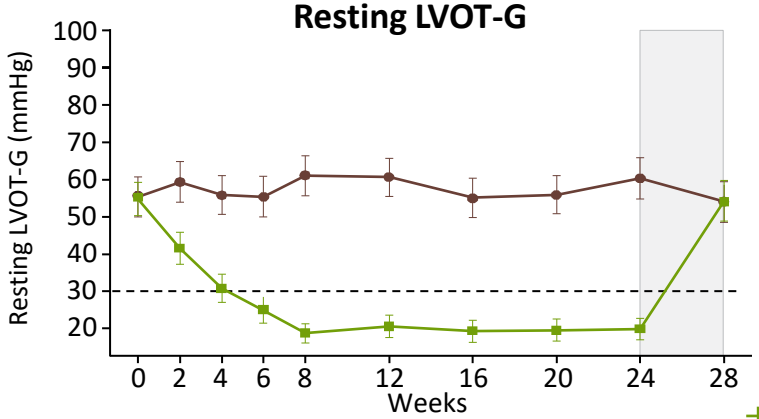

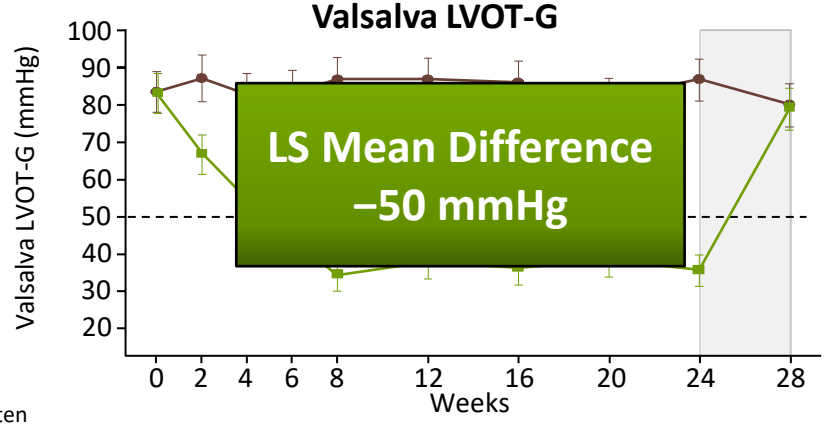

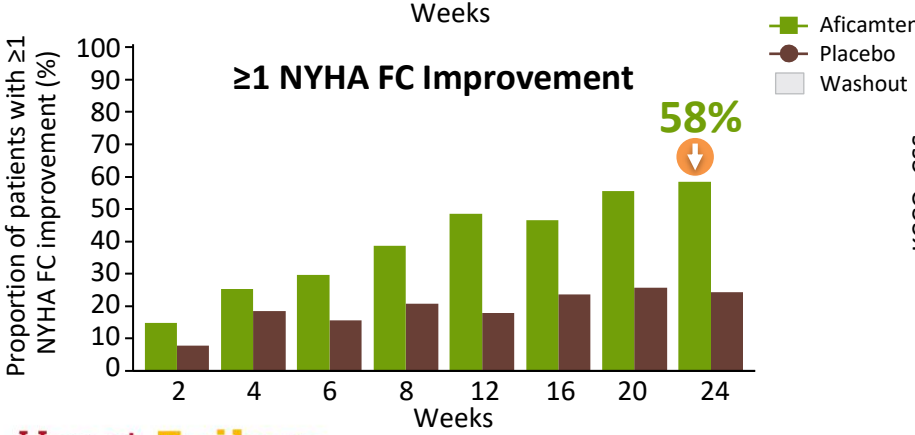

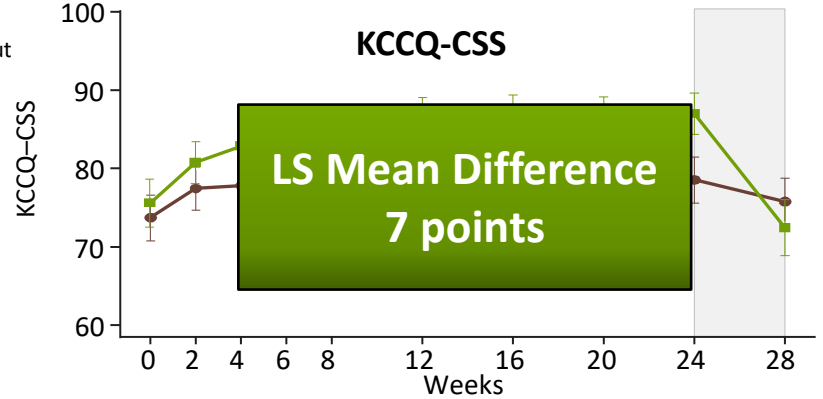

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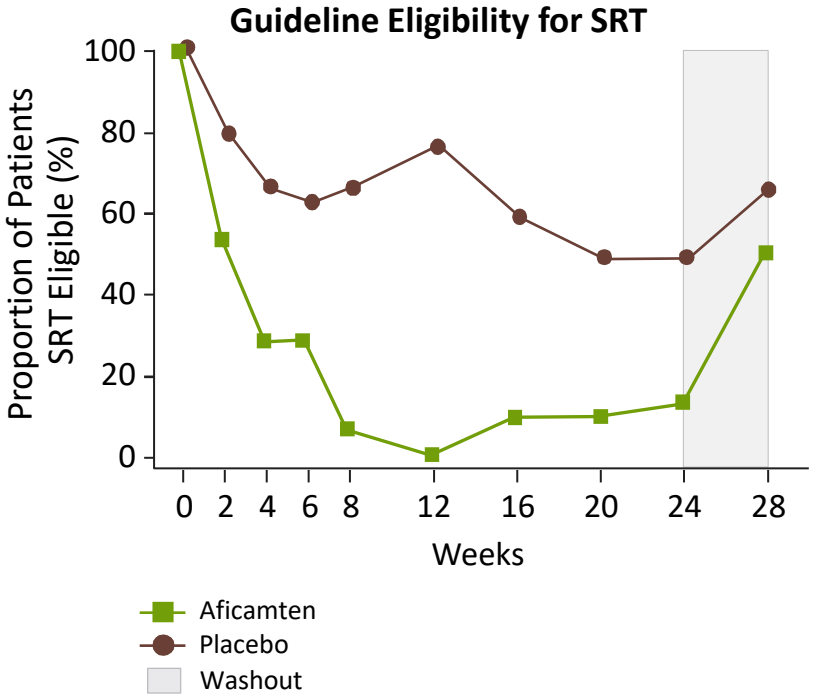
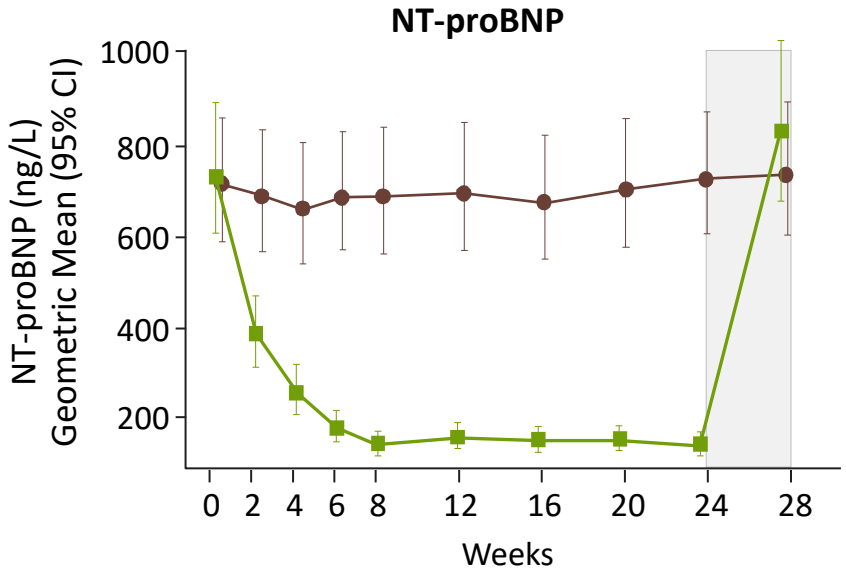
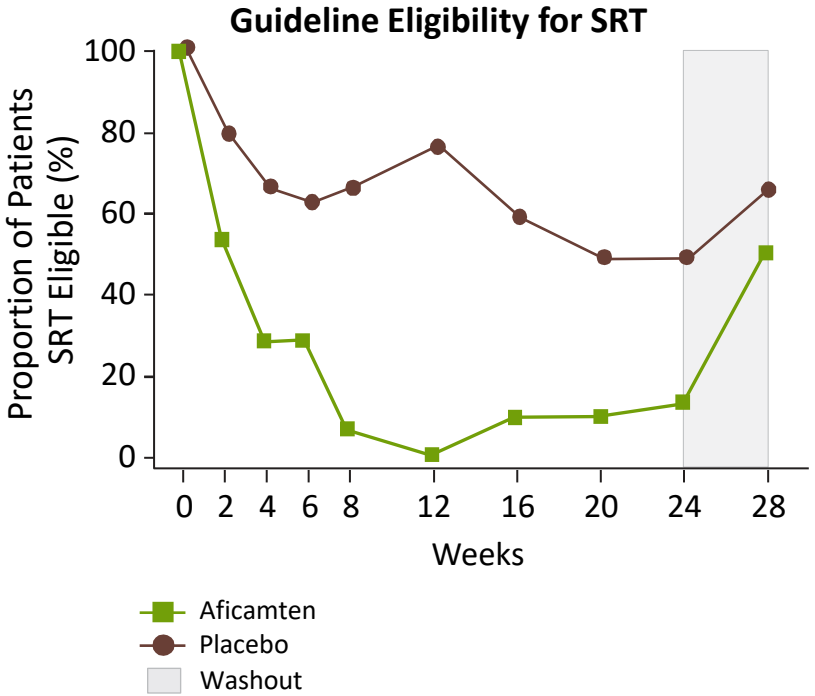


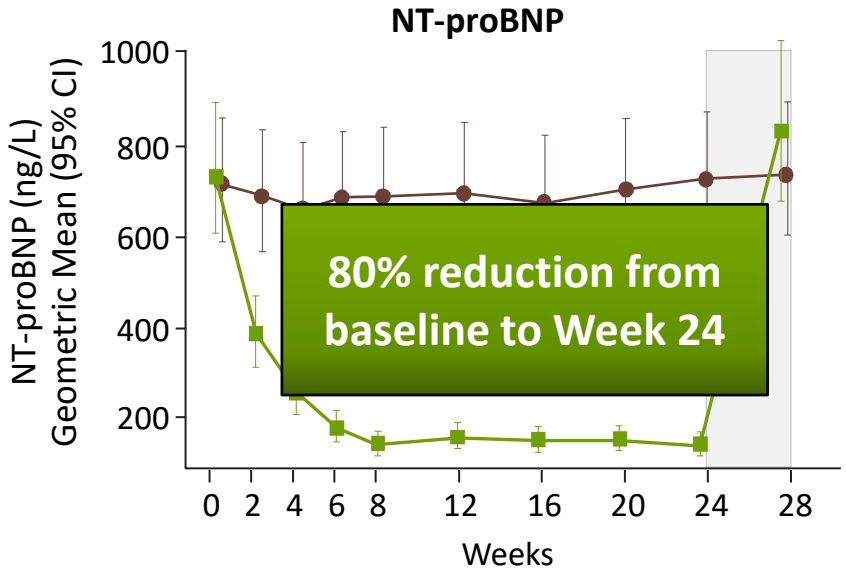


Number of patients

Aficamten	139	141	141	139	139	139	137	139	136	135
Placebo	138	138	139	136	137	135	135	137	134	135

Secondary and Exploratory Endpoints





Number of patients

Aficamten	139	141	141	139	139	139	137	139	136	135
Placebo	138	138	139	136	137	135	135	137	134	135

Exploratory Endpoint

	Aficamten n=142	Placebo n=140
≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA FC improvement *or* ≥3.0 mL/kg/min increase in pVO_2 and no worsening of NYHA FC, n (%)	**60 (42)**	**19 (14)**
≥1.5 mL/kg/min increase in pVO2 and ≥1 NYHA class improvement	44 (31)	9 (6)
≥3.0 mL/kg/min increase in pVO2 and no worsening of NYHA class	37 (26)	13 (9)
Both ≥3.0 mL/kg/min increase in pVO2 and ≥1 NYHA class improvement	21 (15)	3 (2)
Common rate difference vs placebo (95% CI)	**28.7 (18.8, 38.6)**	
***P* value**	**<0.0001**	

Conclusions

- In patients with symptomatic oHCM, treatment with aficamten over 24 weeks resulted in ***clinically meaningful improvements*** in exercise capacity (pVO2)
- Aficamten significantly ***decreased the burden of limiting symptoms*** based on improvement in both KCCQ-CSS and NYHA FC
- Robust functional and symptomatic improvements and relief from obstruction were observed as early as 2 weeks and remained durable throughout the treatment period

SEQUOIA-HCM underscores the clinical efficacy of aficamten in the treatment of patients with symptomatic oHCM

Acknowledgments

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- Participants and their families
- Investigators and study site staff
- Data Monitoring Committee members
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ORIGINAL ARTICLE

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M.S. Maron, A. Masri, M.E. Nassif, R. Barriales-Villa, M. Arad, N. Cardim, L. Choudhury, B. Claggett, C.J. Coats, H.-D. Düngen, P. Garcia-Pavia, A.A. Hagège, J.L. Januzzi, M.M.Y. Lee, G.D. Lewis, C.-S. Ma, M. Michels, I. Olivotto, A. Oreziak, A.T. Owens, J.A. Spertus, S.D. Solomon, J. Tfelt-Hansen, M. van Sinttruije, J. Veselka, H. Watkins, D.L. Jacoby, S.B. Heitner, S. Kupfer, F.I. Malik, L. Meng, A. Wohltman, and T.P. Abraham, for the SEQUOIA-HCM Investigators*