PIONEER-HCM: A Phase 2 study of Mavacamten (formerly MYK-461) in Symptomatic Obstructive Hypertrophic Cardiomyopathy Patients

SB Heitner[1], D Jacoby[2], S Lester[3], A Owens[4], A Wang[5], D Young[6], M Grimm[6], E Green[6], M Semigran[6]

[1]Oregon Health & Science University, [2]Yale School of Medicine, [3]Mayo Clinic Arizona, [4]University of Pennsylvania, [5]Duke University Medical Center, [6]MyoKardia, Inc.

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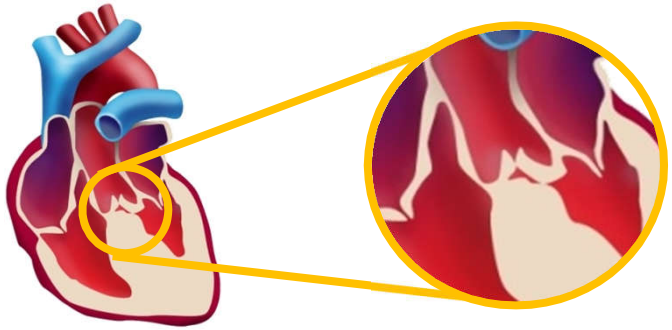
Hypertrophic Cardiomyopathy (HCM)

- HCM is the most common monogenic disease of the myocardium
- HCM is characterized by excessive myocardial contractility, left ventricular hypertrophy and reduced compliance
- Obstructive HCM occurs as a result of asymmetric LVH, abnormal MV and sub-valvular apparatus, and resultant SAM-septal contact[1]



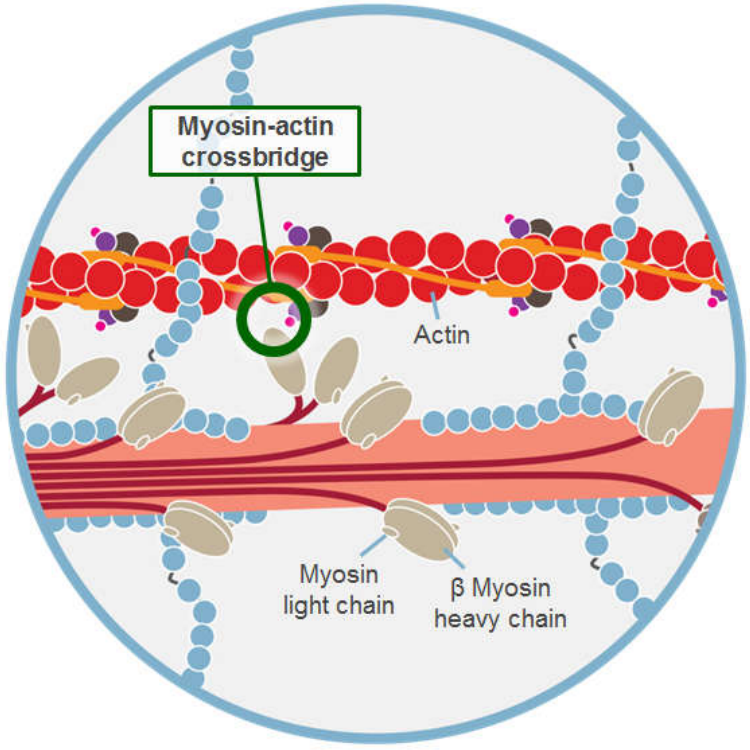
- Earlier onset of severe HF symptoms and/or death vs. non-obstructive HCM[2-3]
- Medical management is limited to drugs (e.g. beta-blockers) or invasive procedures
- Invasive interventions are associated with significant morbidity & mortality[4-5]

1. Gersh et al. Circulation 2011;124: e783–e831. 2. Ommen, S. R. et al. J Am Coll Cardiol 2005;46:470–6 3. Maron, M. S., et al. The New England Journal of Medicine 2003;348(4):295–303 4. Firoozi, S. et al. European Heart Journal 2002;23:1617–1624 5. Kim et al. JAMA Cardiology 2016; 1(3):324-332.

Mavacamten (formerly MYK-461)

- Mavacamten
  - Oral small molecule
  - Selective allosteric modulator of cardiac myosin ATPase
  - In HCM mutant mice, mavacamten prevented hypertrophy, reduced myocyte disarray & interstitial fibrosis compared with placebo[1]

- Phase 1 studies:
  - Dose-dependent reduction in cardiac contractility in volunteers & patients
  - Favorable safety profile observed across a number of doses
  - One SAE observed (vasovagal); all other AEs mild to moderate



1. Green et al. Science 2016; 351:617

PIONEER-HCM: Scientific Hypothesis

Mavacamten, a modulator of cardiac myosin, reduces LVOT gradient in symptomatic obstructive HCM patients

Key Inclusion and Exclusion Criteria & Statistical Plan for Cohort A

Key Inclusion Criteria

- 18-70 years old with symptomatic (NYHA functional class ≥ II) HCM
- LVOT gradient ≥ 30 mmHg (resting) and ≥ 50 mm Hg (post-exercise peak LVOT gradient)
- LVEF ≥ 55%
- Patients discontinued beta-blockers, CCB and disopyramide >14 days prior to screening

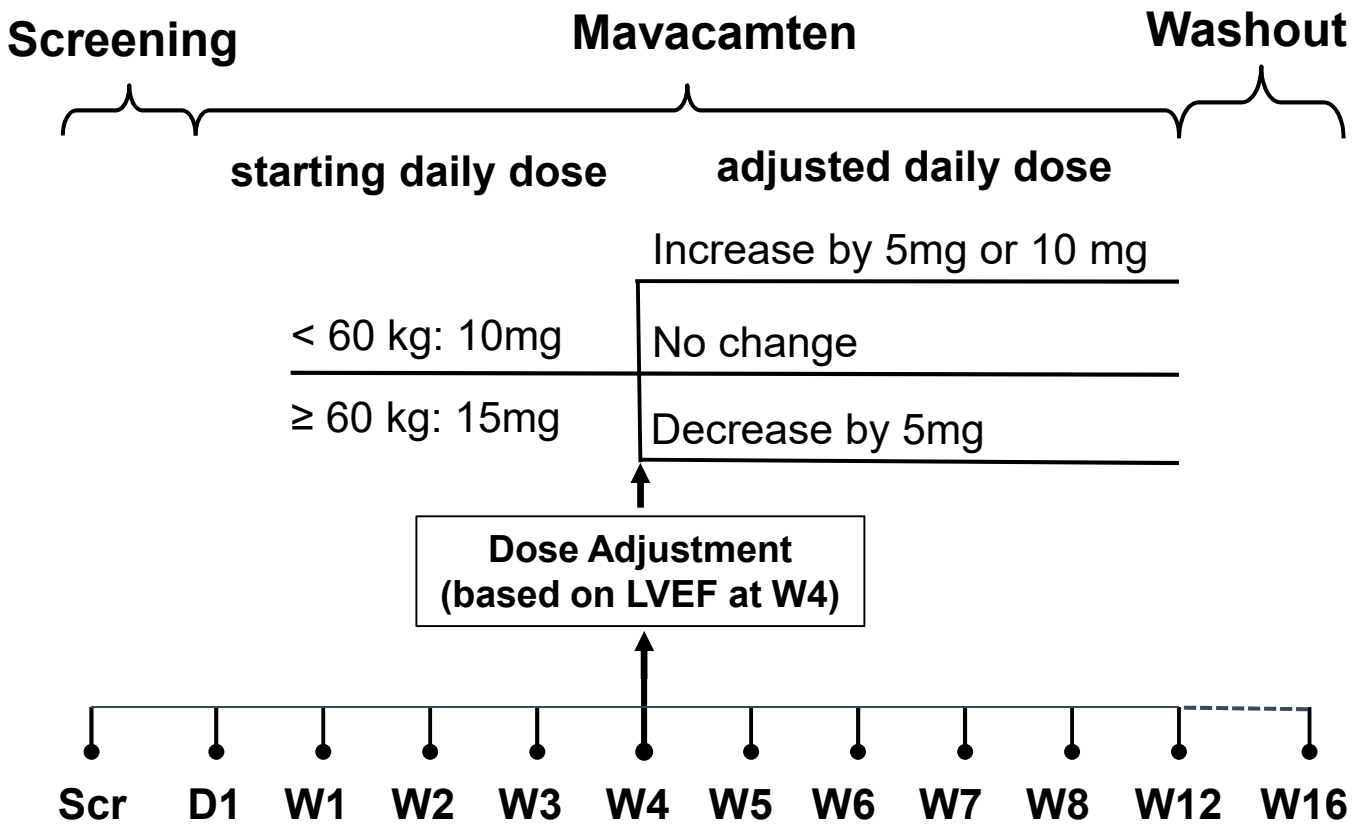
Key Exclusion Criteria

- History of syncope with exercise within the past 6 months
- History of VT or persistent atrial fibrillation or atrial fibrillation at screening
- History of obstructive coronary artery disease

Statistical Analysis Plan

- Within patient change from baseline to week 12 were evaluated using Wilcoxon Signed Rank test against null hypothesis of zero change

PIONEER-HCM: Cohort A Study Design



	Scr	D1	W1	W2	W3	W4	W5	W6	W7	W8	W12	W16
Stress echo	x					x					x	x
CPET		x									x	
Rest echo	x	x	x	x	x	x	x	x	x	x	x	x

W = Week; D = day; Scr = Screening

PIONEER–HCM Trial Endpoints

Primary Endpoint:

- Change in post-exercise peak LVOT gradient from baseline to Week 12

Key Secondary & Exploratory Endpoints:

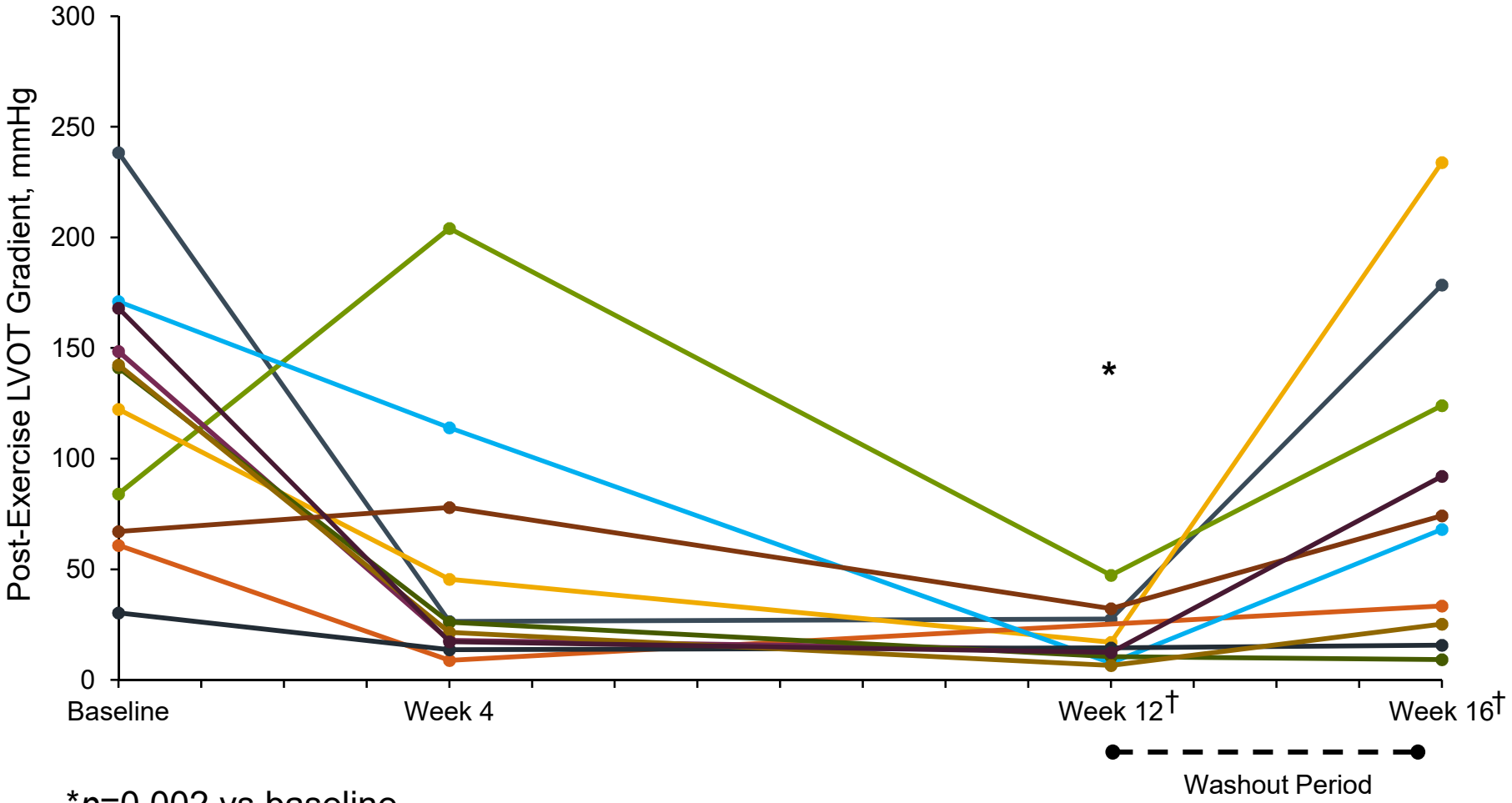
- Proportion of patients achieving post-exercise peak gradient <30 mmHg at Week 12
- Change from Week 12 to Week 16 in post-exercise peak LVOT gradient
- Change in LVEF from baseline to Week 12
- Change in dyspnea symptom score from baseline to Week 12
- Change in pVO2 and VE/VCO2 from baseline to Week 12
- Change in NYHA Class from baseline to Week 12
- Change in N-terminal pro B-type natriuretic peptide (NT-proBNP) from baseline to Week 12

Baseline Characteristics in PIONEER (Part A)

Parameter	Value
Number of patients	N = 11
Number of sites	5
Age, yrs; mean (min-max)	56 (22-70)
Sex, % male	64
NYHA Class, %	64% Class II 36% Class III
Hx of Paroxysmal Atrial Fib Hx of Septal Myectomy Previous β Blocker Therapy	N = 1 N = 1 N = 9

Parameter	Value
Resting LVEF, % mean ± SD	70 ± 7
Exercise LVEF, % mean ± SD	76 ± 8
Resting LVOT Gradient, mmHg mean ± SD	68 ± 34
Exercise LVOT Gradient, mmHg mean ± SD	125 ± 60
Peak VO_2, mL/kg/min mean ± SD	20.7 ± 7.4

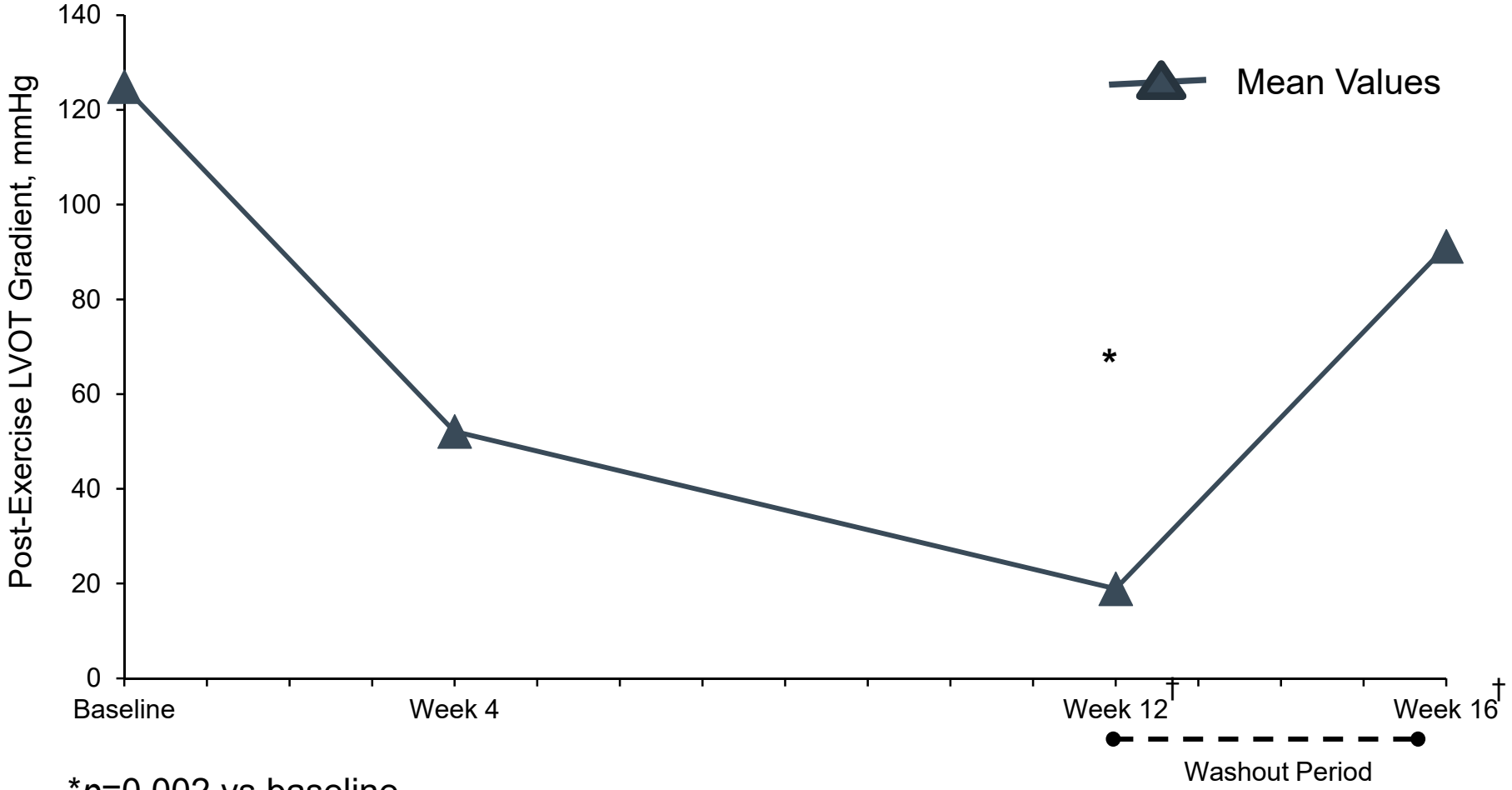
Primary Endpoint:
Rapid Reduction in Post-Exercise LVOT Gradient



*p=0.002 vs baseline

† N<11 due to pt who terminated study early or missing data

Primary Endpoint:
Rapid Reduction in Post-Exercise LVOT Gradient



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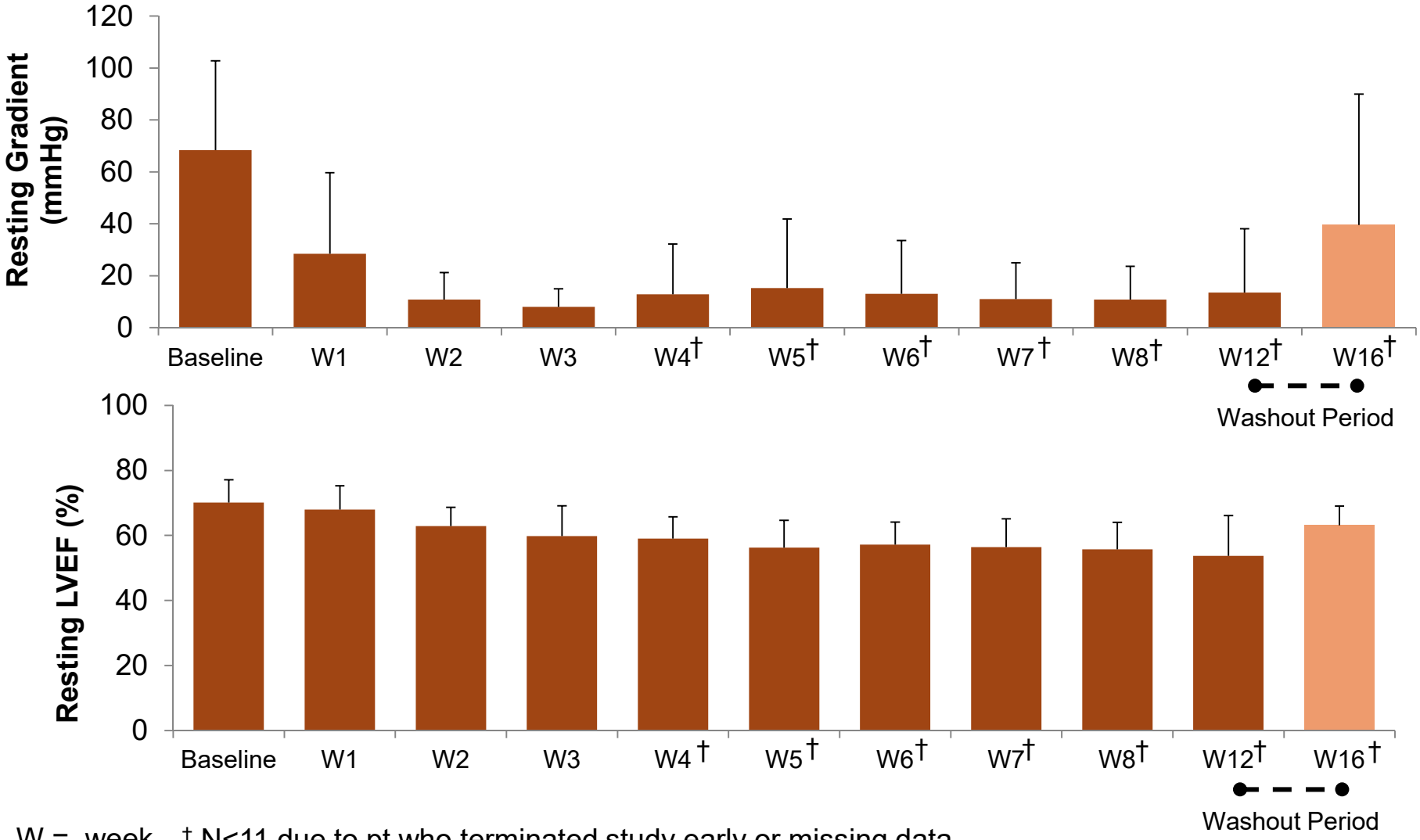
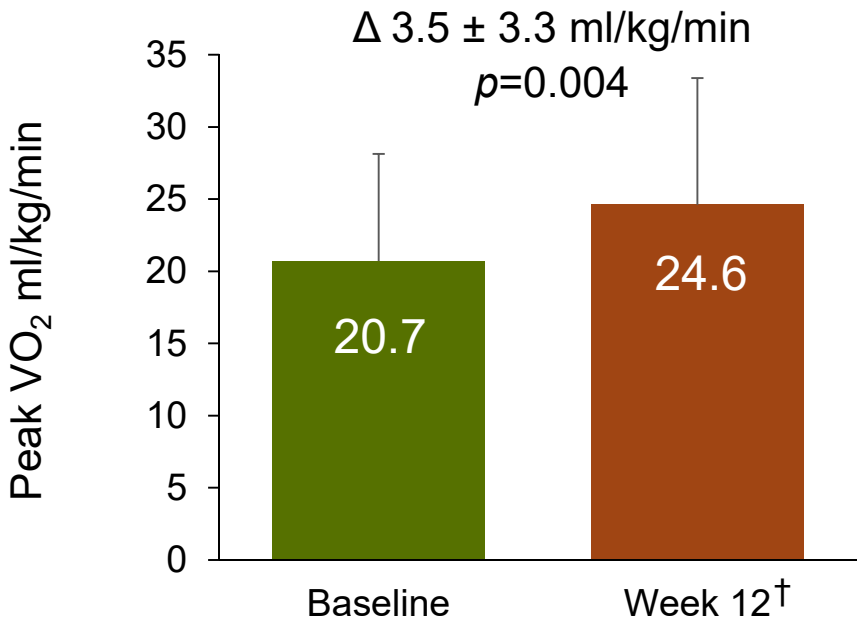
Concordant Change in Resting LVOT Gradient and EF



W = week † N<11 due to pt who terminated study early or missing data

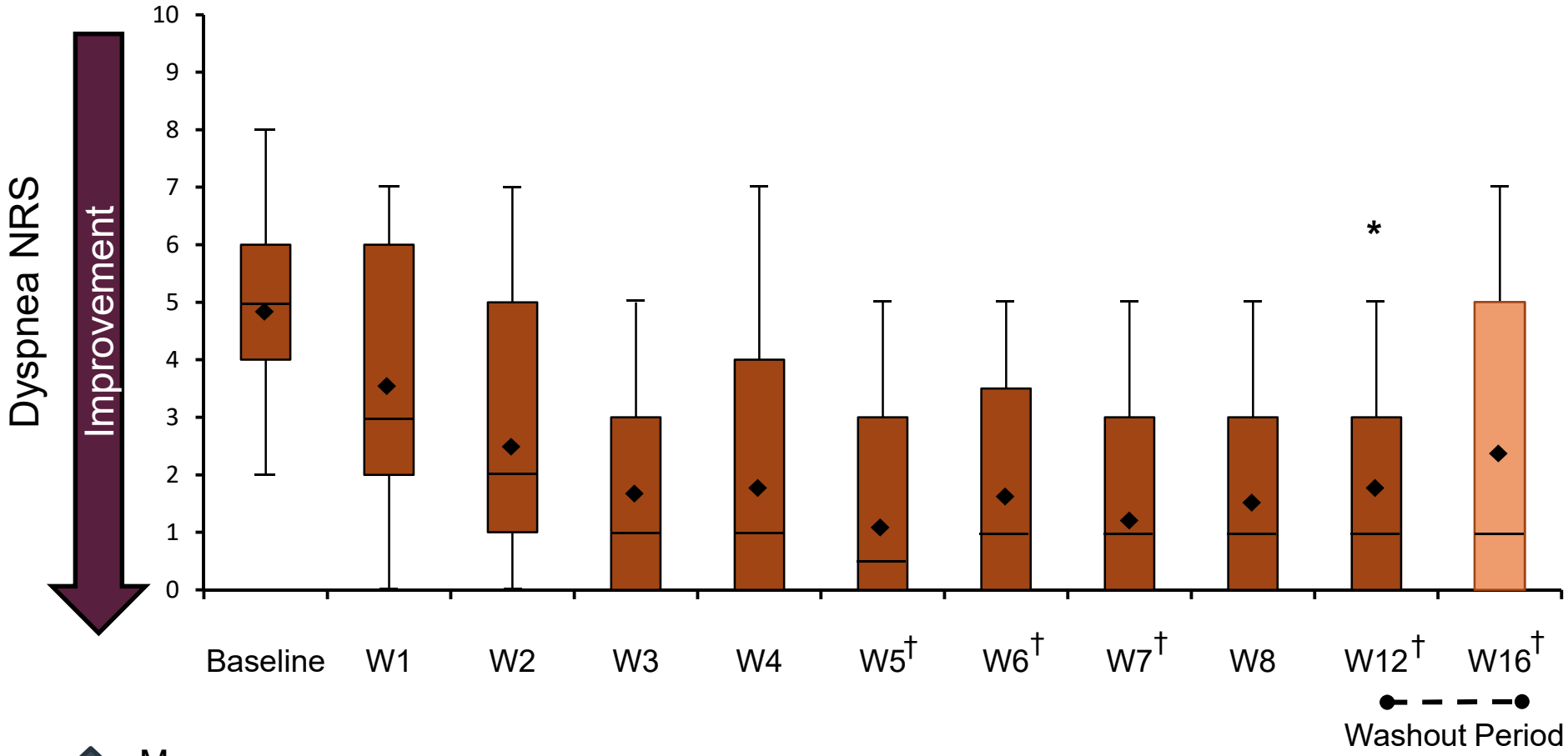
Significant Improvement in Peak VO_2 by Week 12



Additional CPET Parameters	Baseline	Week 12	Change	*p*-value
VE/VCO_2	32.2 ± 5.44	30.3 ± 6.10	-2.19 ± 5.46	0.164
Circulatory Power (mm Hg·mLO2·kg−1·min−1)	3276 ± 1535	4400 ± 2040	1075 ± 932	0.0098

† N<11 due to pt who terminated study early

Rapid Improvement in Dyspnea Over Time



◆ Mean
— Median
W = week

*p=0.002 vs baseline

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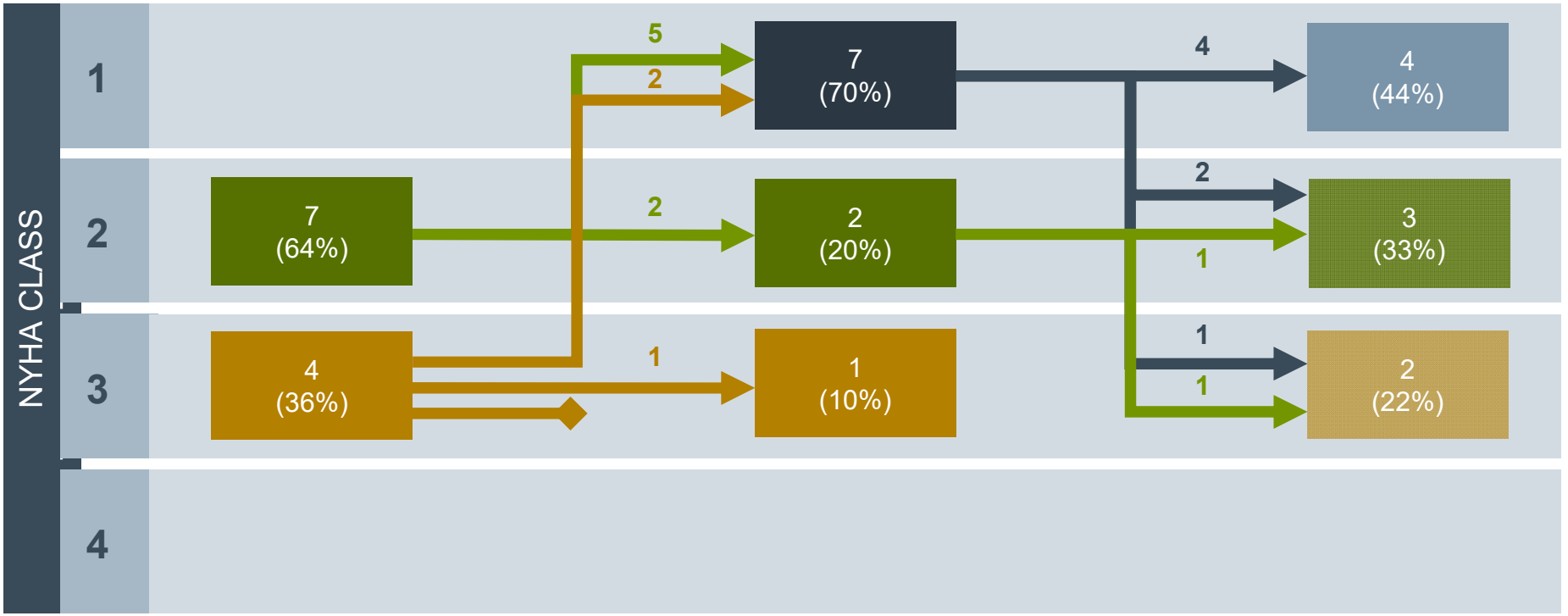
Improvement in NYHA Functional Class



Baseline
N=11

Week 12
N=10 †

Week 16
N=9 †

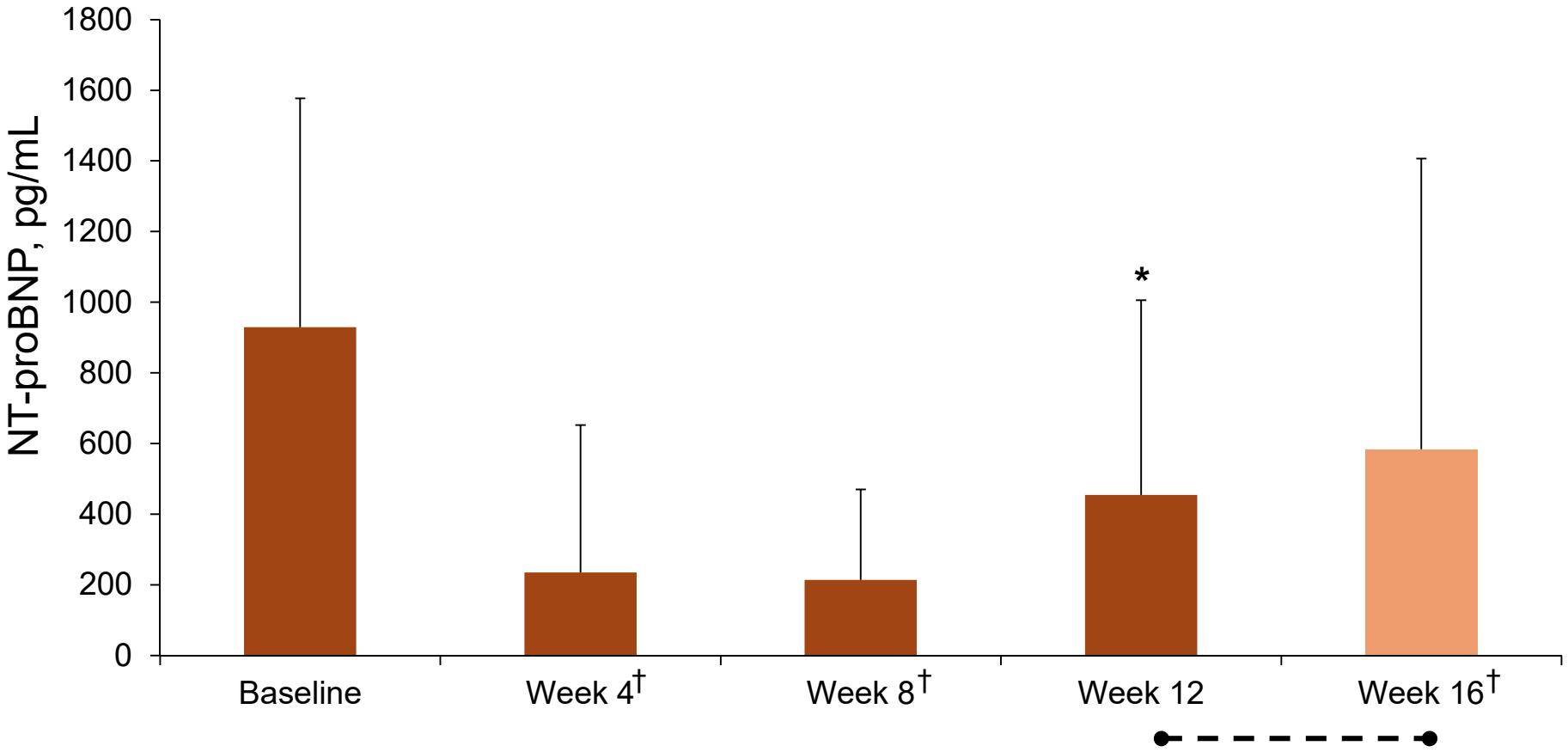
Washout Period

Mean change -0.9 ± 0.7 W12 vs baseline; *p*=0.016

- 5 subjects with 1 class improvement
- 2 subjects with 2 class improvement

† N<11 due to pt who terminated study early or missing data

Change in NT-proBNP



**p*=0.08

† N<11 due to pt who terminated study early or missing data

Safety Events

- Most AEs were mild (77%) to moderate (21%)
- Most AEs were unrelated to mavacamten (64%)
- One SAE
  - Hx of paroxysmal AF
  - Withdrawal of β blocker and disopyramide to participate in the study
  - Pt cardioverted, but AF (2nd AE) recurred requiring hospitalization and anti-arrhythmic therapy
  - Pt elected to stop study drug at week 4
- No increase in hs-troponin
- Independent Data Monitoring Committee found no safety concerns

Non-Serious Adverse Events

	# of events	# assessed related to study drug	# of patients
Headache	4	1	4
LVEF Reduction	3	3	3
Nausea	3	1	2
Atrial Fibrillation	2	1	2
Dizziness	2	0	1
Dyspnea Exertional	2	1	2
Fatigue	2	0	2
Peripheral Edema	2	2	1
Rash	2	0	2
URTI	2	0	2
UTI	2	0	2

URTI = upper respiratory tract infection; UTI = urinary tract infection;

Summary

- All patients had a reduction in post-exercise LVOT gradient
  - All 10 achieved ≤ 50 mmHg; 8 of 10 patients ≤ 30 mmHg
- All patients had a rapid reduction in resting LVOT gradient by week 2
- Peak VO2, NYHA class, dyspnea NRS and NT-pro BNP improved with mavacamten treatment
- Reversibility of mavacamten treatment effect was observed during washout period (Week 12 to Week 16)
- Most adverse events were mild to moderate & unrelated to mavacamten

Conclusion

Mavacamten reduced post- exercise LVOT gradient to below hemodynamic significance in symptomatic oHCM

Global Phase 3 Trial Currently Being Planned (EXPLORER-HCM)

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Back-up slides

Studies Using Peak VO2 as an Endpoint

Study	Disease	n	Intervention	Change in peak VO_2 mL/kg/min
Firoozi et al. EHJ 2002	HCM	24	Myectomy	**6.7**
Firoozi et al. EHJ 2002	HCM	20	ASA	**3.1**
Malek et al. EJHF 2008	HCM	23	ASA	**4**
Abozguia et al. Circ 2010	HCM	46	PEX	**1.4**
Saberi et al. JAMA 2017	HCM	113	Exercise	**1.3**
Swank et al. Circ HF 2012	HFrEF	1620	Exercise	**0.4**
Cazeau et al. NEJM 2001	HFrEF	38	BiV Pacing	**1.2**