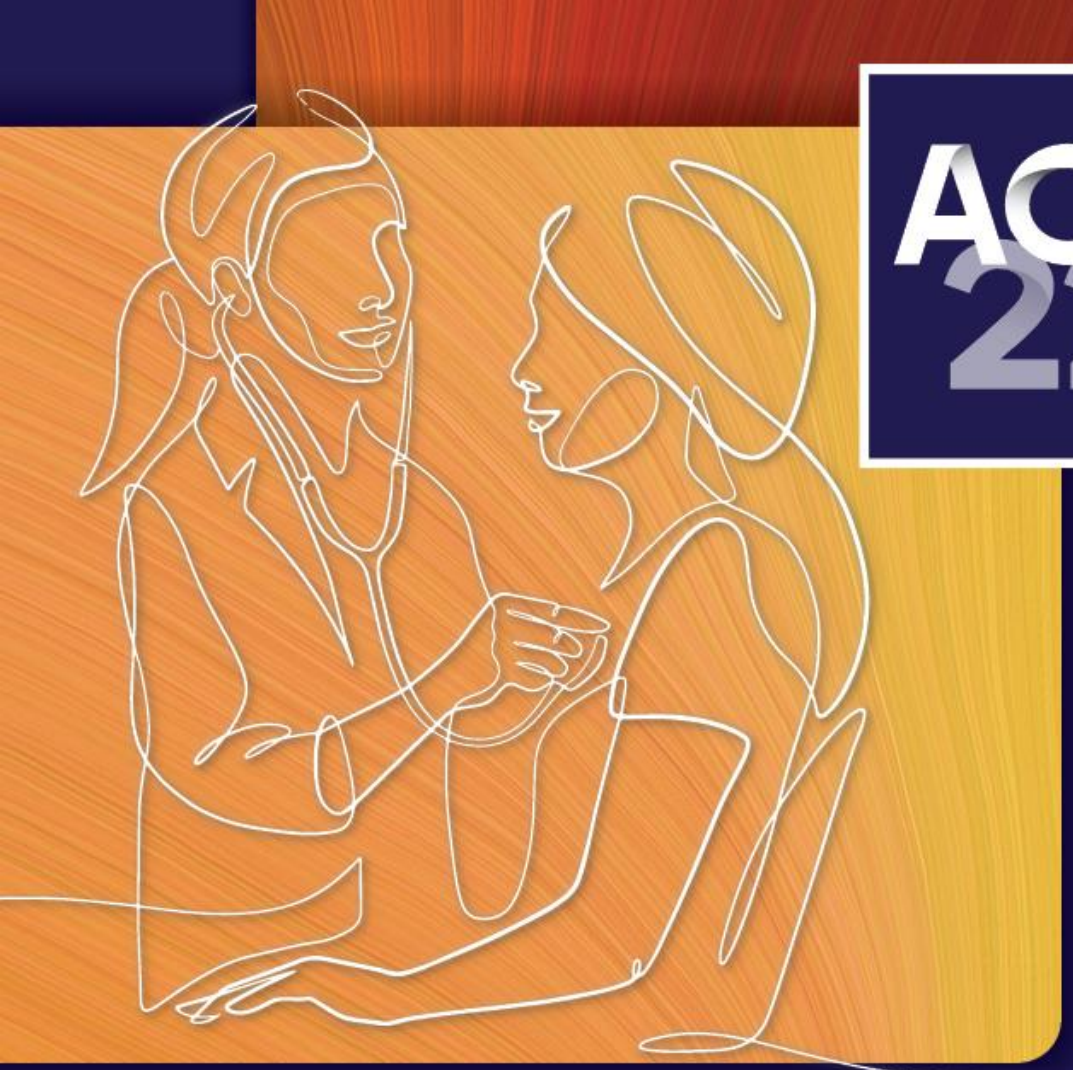


ACC 22

TRANSFORMING CARDIOVASCULAR CARE FOR YOU. FOR YOUR TEAM. FOR YOUR PATIENTS.

AMERICAN COLLEGE of CARDIOLOGY

The Effect of Omecamtiv Mecarbil on Exercise Capacity in Chronic Heart Failure with Reduced Ejection Fraction: The METEORIC-HF Study

G. Michael Felker, MD, MHS
Professor of Medicine
Duke Clinical Research Institute

on behalf of the METEORIC-HF Investigators

@DukeHFDoc

Disclosures

METEORIC-HF

- METEORIC-HF was funded by Cytokinetics, Amgen, and Servier
- Presenter disclosures:
  - *Employment:* Duke University
  - *Grant Support:* NHLBI, AHA, Novartis, Merck, Bayer, BMS, Cytokinetics, CSL-Behring
  - *Consulting:* Novartis, Amgen, Medtronic, BMS, Cytokinetics, Abbott, Cardionomic, American Regent, Reprieve, Boehringer Ingelheim, Astra Zeneca, Sequana, Whiteswell, Myovant
  - *Endpoint Adjudication Committees/DSMBs*: Amgen, Merck, Medtronic, EBR Systems, V-Wave, LivaNova, Rocket Pharma, Seimens

Background

METEORIC-HF

- Exercise intolerance is a cardinal manifestation of heart failure but is not improved by current medical therapies

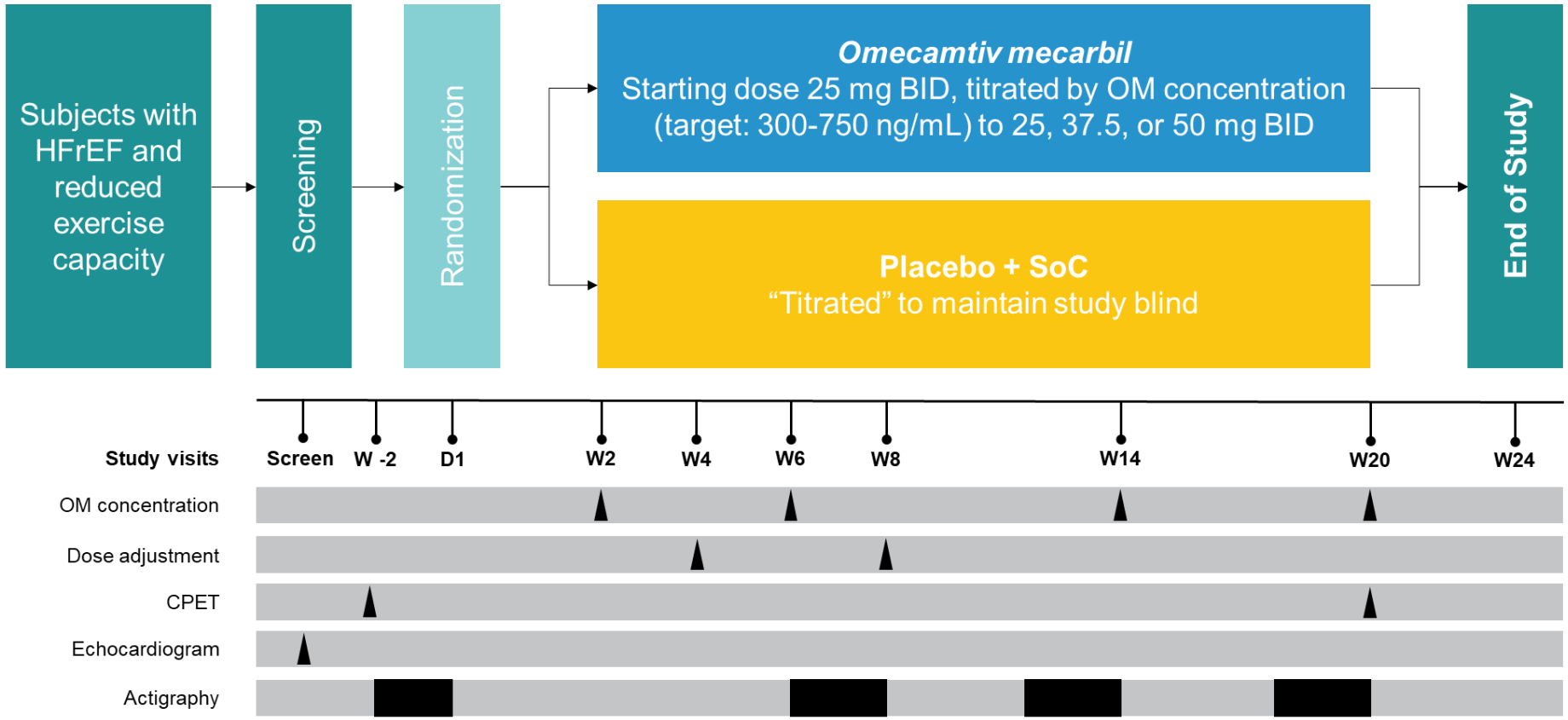
- Omecamtiv mecarbil is a novel selective cardiac myosin activator that increases cardiac performance and improves outcomes in patients with heart failure and reduced ejection fraction (HFrEF)

- The METEORIC-HF study (NCT03759392) was designed to test the hypothesis that omecamtiv mecarbil can improve exercise capacity in patients with HFrEF

Study Design

METEORIC-HF

Double-blind, placebo-controlled, multi-center randomized clinical trial



Lewis, GD et al. Circulation: Heart Failure 2022

Inclusion and Exclusion Criteria

METEORIC-HF

Key inclusion criteria

- Age ≥18 to ≤85 years
- Chronic NYHA class II-III heart failure
- LVEF ≤ 35% within 12 months
- On maximally tolerated HF therapies if not contraindicated
- NT-proBNP ≥ 200 pg/mL
- pVO_2 ≤ 75% of the age predicted normal value on screening CPET
- RER ≥ 1.05 on screening CPET

Key exclusion criteria

- Decompensated HF within prior 3 months
- SBP > 140 or < 85 mmHg
- Resting HR > 90 or < 50 bpm
- Hemoglobin <10.0 g/dL
- eGFR <30 mL/min per 1.73 m2
- Severe uncorrected valvular heart disease
- Paroxysmal atrial fibrillation or flutter requiring treatment within prior 6 months
- Untreated severe ventricular arrhythmias
- Symptomatic bradycardia, second-degree Mobitz type II, or third-degree heart block

Lewis, GD et al. Circulation: Heart Failure 2022

Endpoints and Statistical Approach

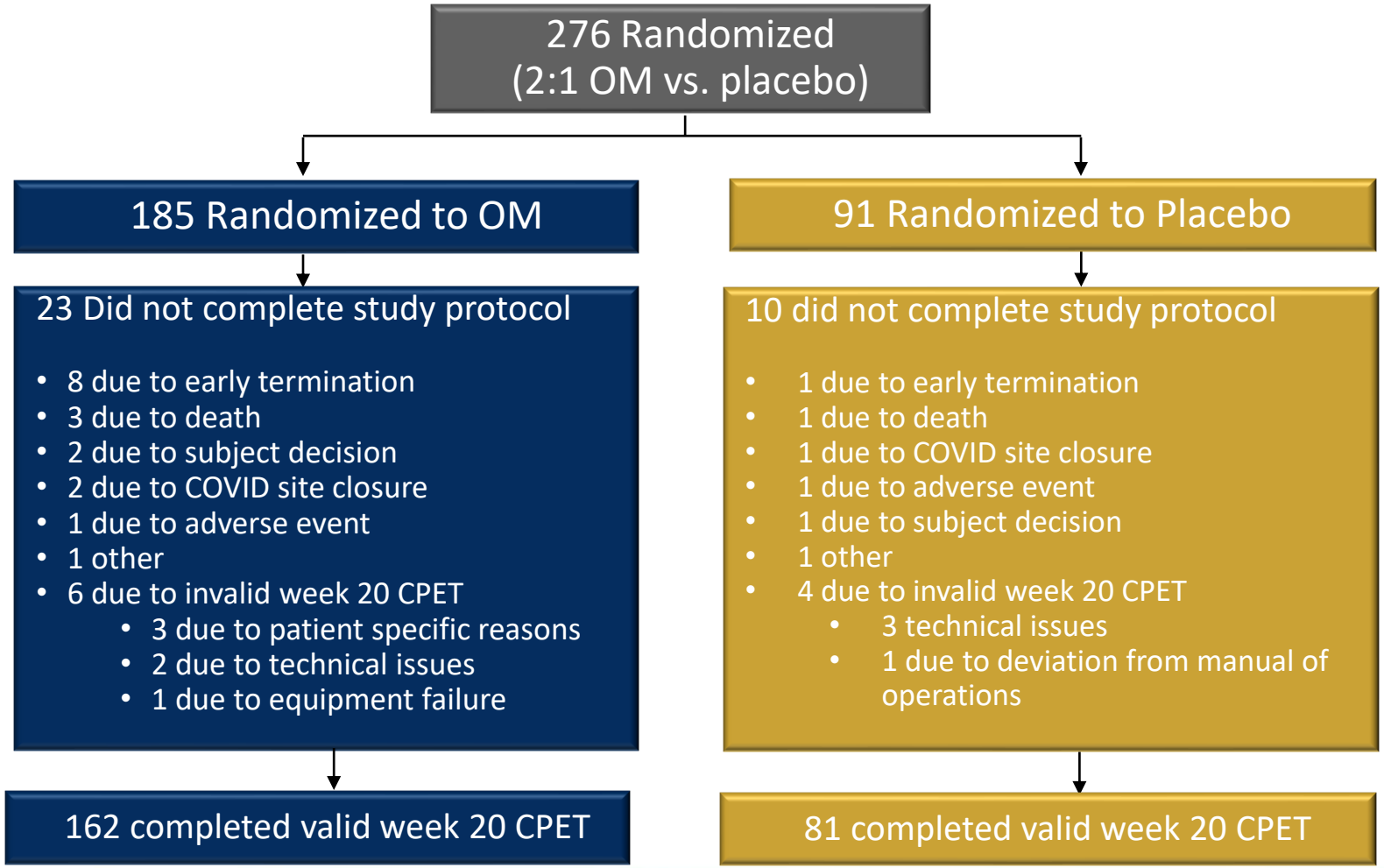
METEORIC-HF

- **Primary Endpoint**
  - Change in peak oxygen consumption (pVO_2) from baseline to 20 weeks
- **Secondary Endpoints**
  - Change in total workload during exercise from baseline to 20 weeks
  - Change in ventilatory efficiency (V_E/VCO_2 slope) from baseline to 20 weeks
  - Change in daily physical activity by accelerometry from baseline to 20 weeks
- **Statistical Considerations**
  - Powered to detect a difference in pVO_2 of ≥ 1.0 mL/kg/min for omecamtiv mecarbil vs placebo
  - Assumed 15% of participants unable to complete week 20 CPET
  - Primary analysis ANCOVA with multiple imputation for patients with missing week 20 CPET

Lewis, GD et al. Circulation: Heart Failure 2022

RESULTS

Participant Disposition



Baseline Characteristics

	Omecamtiv Mecarbil (N=185)	Placebo (N=91)	All (N=276)
Demographics and Medical History			
Age, years	63 (10)	64 (11)	64 (10)
White, n(%)	163 (88%)	82 (90%)	245 (89%)
Women, n(%)	27 (15%)	15 (16%)	42 (15%)
SBP (mmHg)	115 (18)	113 (17)	114 (17)
Heart Rate (bpm)	69 (10)	67 (11)	69 (10)
Ischemic HF, n (%)	117 (63%)	48 (53%)	165 (60%)
Atrial Fibrillation, n (%)	26 (14%)	12 (13%)	38 (14%)
LVEF (%)	27 (7)	27 (6)	27 (6)
NYHA Class II, n (%)	143 (77%)	74 (81%)	217 (79%)
eGFR (mL/min/1.73m^2)	66 (21)	68 (22)	67 (21)
NT-proBNP (pg/mL)	1343 (1854)	1271 (1490)	1320 (1740)

*Values are mean (SD) or N (%)

	Omecamtiv Mecarbil (N=185)	Placebo (N=91)	All (N=276)
Medical and Device Therapy			
Beta Blocker, n (%)	175 (95%)	90 (99%)	265 (96%)
MRA, n (%)	131 (71%)	67 (74%)	198 (72%)
ACEi/ARB/ARNi, n (%)	176 (96%)	85 (93%)	261 (95%)
ARNi, n (%)	124 (67%)	58 (64%)	182 (66%)
SGLT2i, n (%)	31 (17%)	19 (21%)	50 (18%)
Digoxin, n (%)	27 (15%)	8 (9%)	35 (13%)
CRT-D, n (%)	39 (21%)	27 (30%)	66 (24%)
ICD only, n(%)	107 (58%)	42 (46%)	149 (54%)

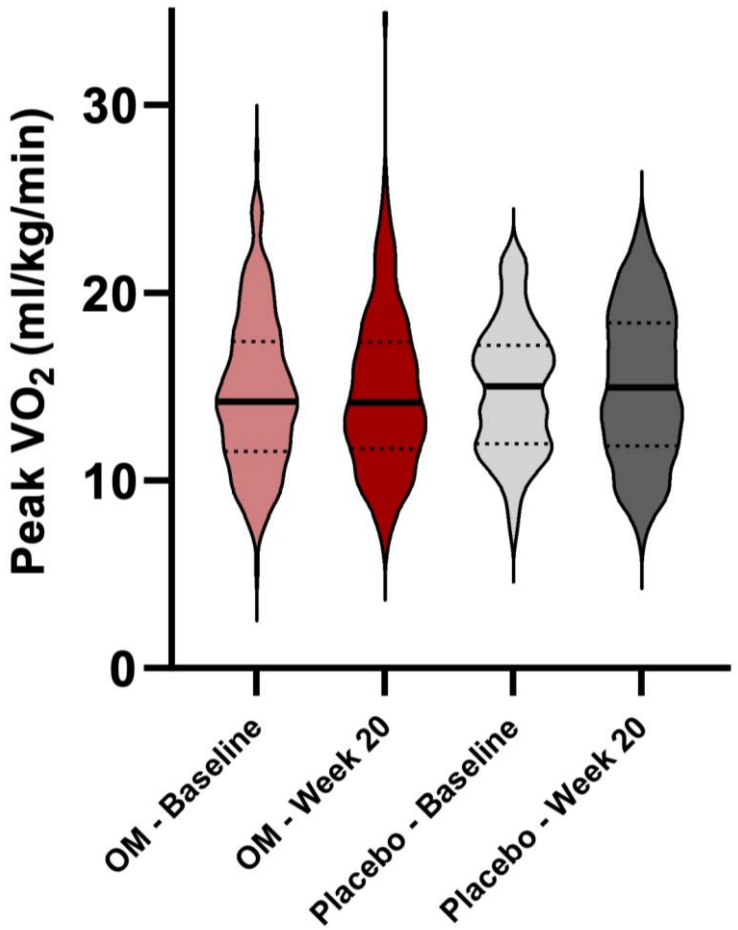
Background HF therapy in METEORIC-HF was better than any prior global HF trial

Baseline Exercise Parameters

	Omecamtiv Mecarbil (N=185)	Placebo (N=91)	All (N=276)
CPET Modality - Cycle	158 (85%)	76 (84%)	234 (85%)
RER ≥ 1.15, n (%)	119 (64%)	59 (65%)	178 (65%)
Peak RER	1.19 (0.10)	1.21 (0.11)	1.20 (0.10)
Peak VO_2 (ml/min/kg)	14.7 (4.1)	14.9 (3.4)	14.7 (3.9)
Total Workload (watts)	100 (37)	100 (31)	100 (35)
V_E/VCO_2 slope	35.5 (8.1)	35.3 (7.3)	35.5 (7.8)

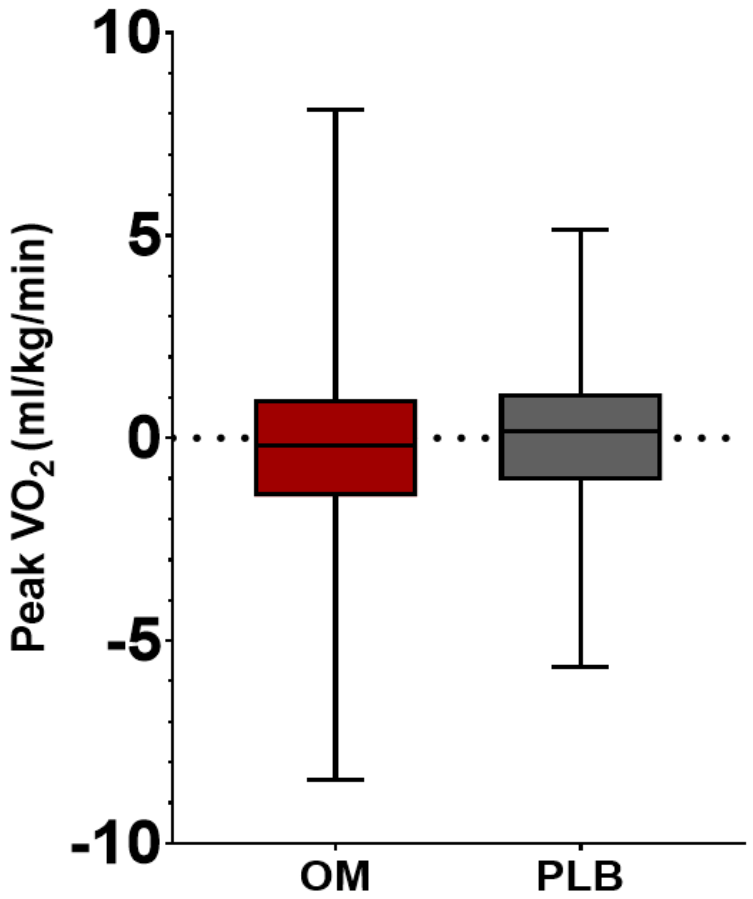
*Values are mean (SD) or N (%)

Peak VO_2 : Baseline and Week 20 Data



		Omecamtiv mecarbil	Placebo
		(N=185)	**(N=91)**
Baseline	N	185	91
	Mean (SD)	14.7 (4.1)	14.9 (3.4)
Week 20	N	162	81
	Mean (SD)	14.8 (4.4)	15.1 (4.0)
Δ from Baseline	N	162	81
	Mean (SD)	-0.2 (2.2)	0.2 (2.1)

Primary Endpoint: Change in Peak VO_2

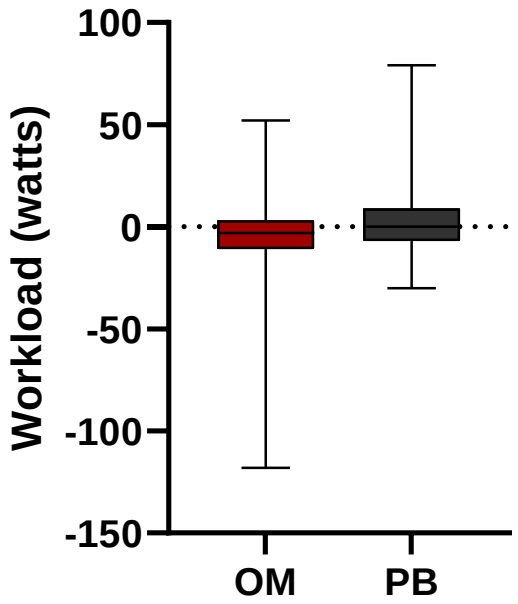


	Omecamtiv Mecarbil	Placebo
LSM (SE)	-0.24 (0.17)	0.21 (0.24)
LSM Diff (95%CI)	**-0.45 (-1.0, 0.13)**	
p-value	**0.13**	

Secondary Endpoints

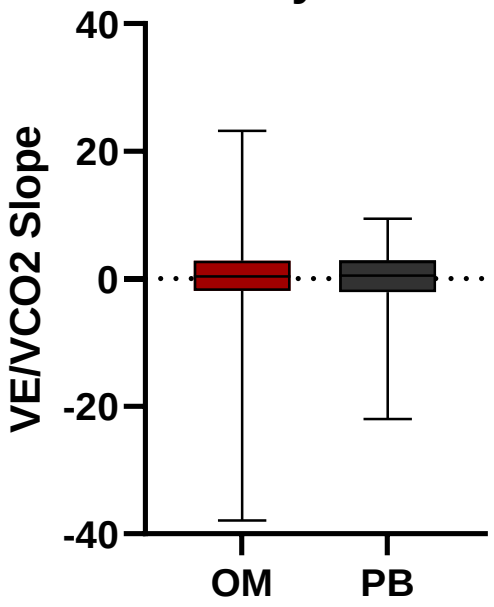
METEORIC-HF

Change in Workload



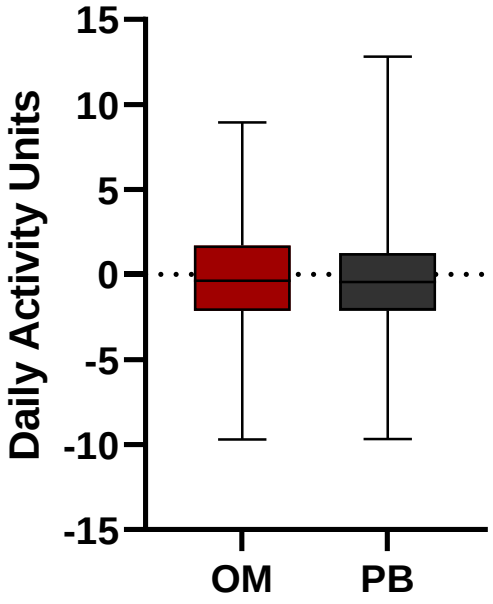
Mean difference: -5.4
P-value: 0.025

Change in Ventilatory Efficiency



Mean difference: 0.41
P-value: 0.51

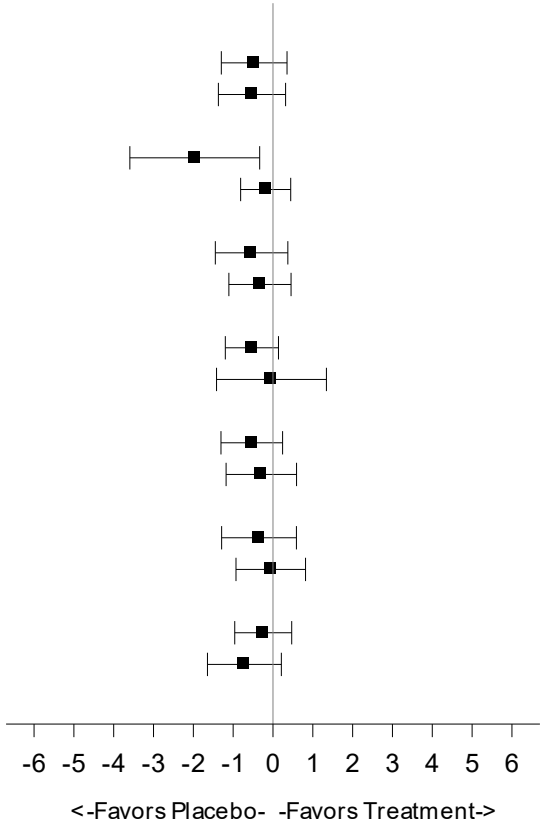
Change in Actigraphy



Mean difference: 0.30
P-value: 0.54

Subgroup Analyses

	No.of Patients (placebo/ omecamtiv)
Baseline RER	
<= Median (1.18)	48/98
> Median (1.18)	43/87
Persistent Atrial Fibrillation	
Yes	13/29
No	78/156
Age Group	
< 65 Years	42/98
>= 65 Years	49/87
NYHA Class at Baseline	
Class II	74/143
Class III	17/42
Left Ventricular Ejection Fraction at BL	
<= Median (28 %)	51/95
> Median (28 %)	40/90
NT-proBNP at Baseline	
<= Median (710.5 pg/mL)	37/80
> Median (710.5 pg/mL)	41/76
pVO□at Baseline	
<= Median (14.3 mL/kg/min)	44/94
> Median (14.3 mL/kg/min)	47/91



Adjudicated Safety Events

METEORIC-HF

Safety Endpoints, n(%)	OM (N = 185)	Placebo (N = 91)	Overall
Adverse events	126 (68%)	58 (64%)	184 (67%)
Serious adverse events	30 (16%)	13 (14%)	43 (16%)
Permanent study drug discontinuation	12 (6%)	4 (4%)	16 (6%)
Heart Failure Event	9 (5%)	4 (4%)	13 (5%)
Death	3 (2%)	1 (1%)	4 (1%)
Stroke	1 (0.5%)	1 (1%)	2 (1%)
MI Event/Hospitalization for UA	0 (0%)	1 (1%)	1 (0.4%)

Conclusions

METEORIC-HF

- In well-treated patients with chronic HFrEF, omecamtiv mecarbil did not improve measures of exercise capacity over 20 weeks compared to placebo
- Consistent with prior studies of omecamtiv mecarbil, overall safety was comparable to placebo, without safety signals related to peak exercise
- Identifying medical therapies that safely improve exercise capacity in HFrEF remains an unmet challenge

Acknowledgements

- **Steering Committee**: Gregory D. Lewis, MD (Co-Chair), G. Michael Felker, MD, MHS (Co-Chair), Adriaan A. Voors, MD, PhD; Alain Cohen-Solal, MD, PhD; Marco Metra, MD; David J. Whellan, MD MHS; Justin A. Ezekowitz, MBBCh MSc; Michael Böhm, MD; John R. Teerlink, MD; Kieran F. Docherty, BSc, MB ChB
- **Exercise Core Laboratory (MGH):** Gregory D. Lewis, MD, Anastasia Christ, Shana McGinnis
- **Clinical Events Committee (DCRI):** Renato D. Lopes, MD, PhD (Chair), Derek Chew, MD, Bradley Kolls, MD, David Kong, MD, Robert McGarrah, MD, Thomas Povsic, MD, Marc Samsky. MD, Shreyansh Shah, MD
- **Study Sponsor:** Punag Divanji, MD; Stephen B. Heitner, MD; Stuart Kupfer, MD; Fady I. Malik MD, PhD; Lisa Meng, PhD; Amy Wohltman, Farah Gowgani, Govini Mani, PhD, Siddique Abbasi, MD
- Investigators and study staff at 64 sites in 9 countries
- **276 research participants**