A Phase 2 Study of Intravenous Omecamtiv Mecarbil, A Novel Cardiac Myosin Activator, In Patients With Acute Heart Failure

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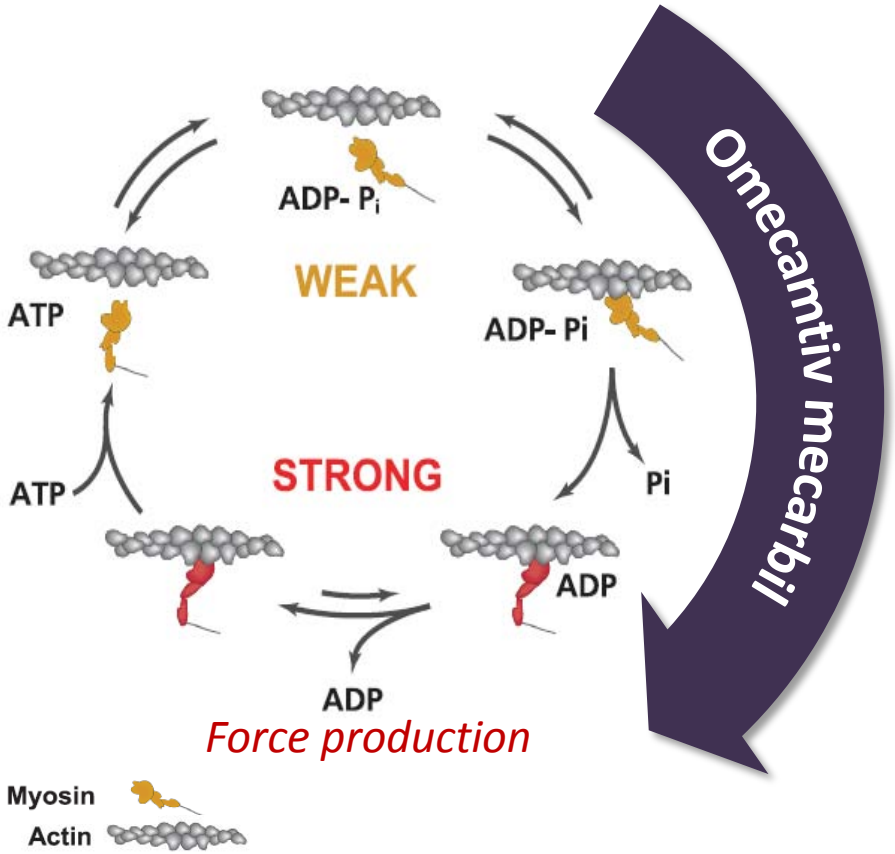
on behalf of the ATOMIC-AHF Investigators and Patients

DECLARATION OF INTEREST

- Research contracts
- Consulting/Royalties/Owner/ Stockholder of a healthcare company

Omecamtiv Mecarbil (OM) is a Novel Selective Cardiac Myosin Activator

Mechanochemical Cycle of Myosin



Omecamtiv mecarbil increases the entry rate of myosin into the tightly-bound, force-producing state with actin

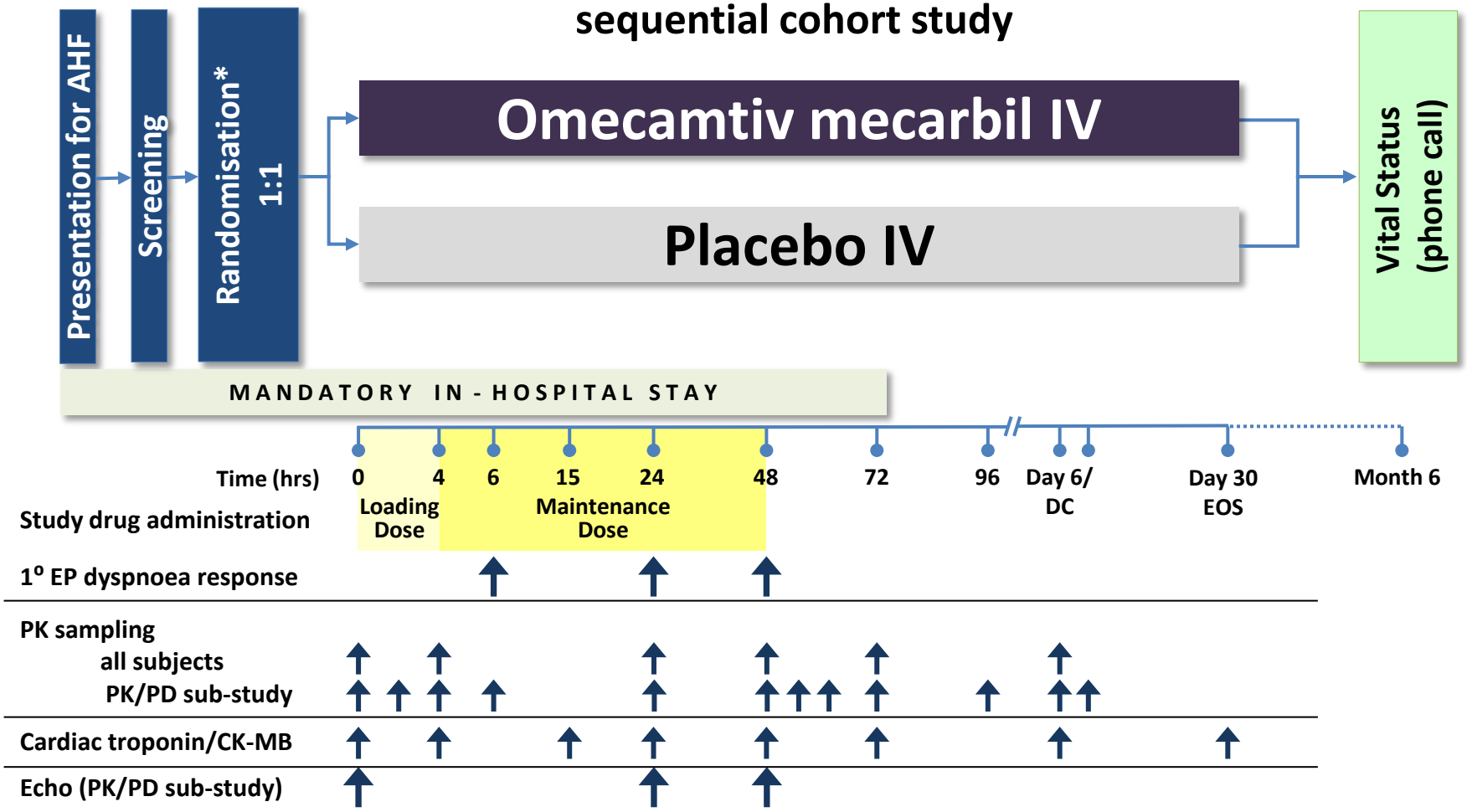
"More hands pulling on the rope"

- Increases duration of systole
- Increases stroke volume
- No increase in myocyte calcium
- No change in dP/dt_{max}
- No increase in MVO_2

Malik FI, *et al.* *Science* 2011; 331:1439-43.

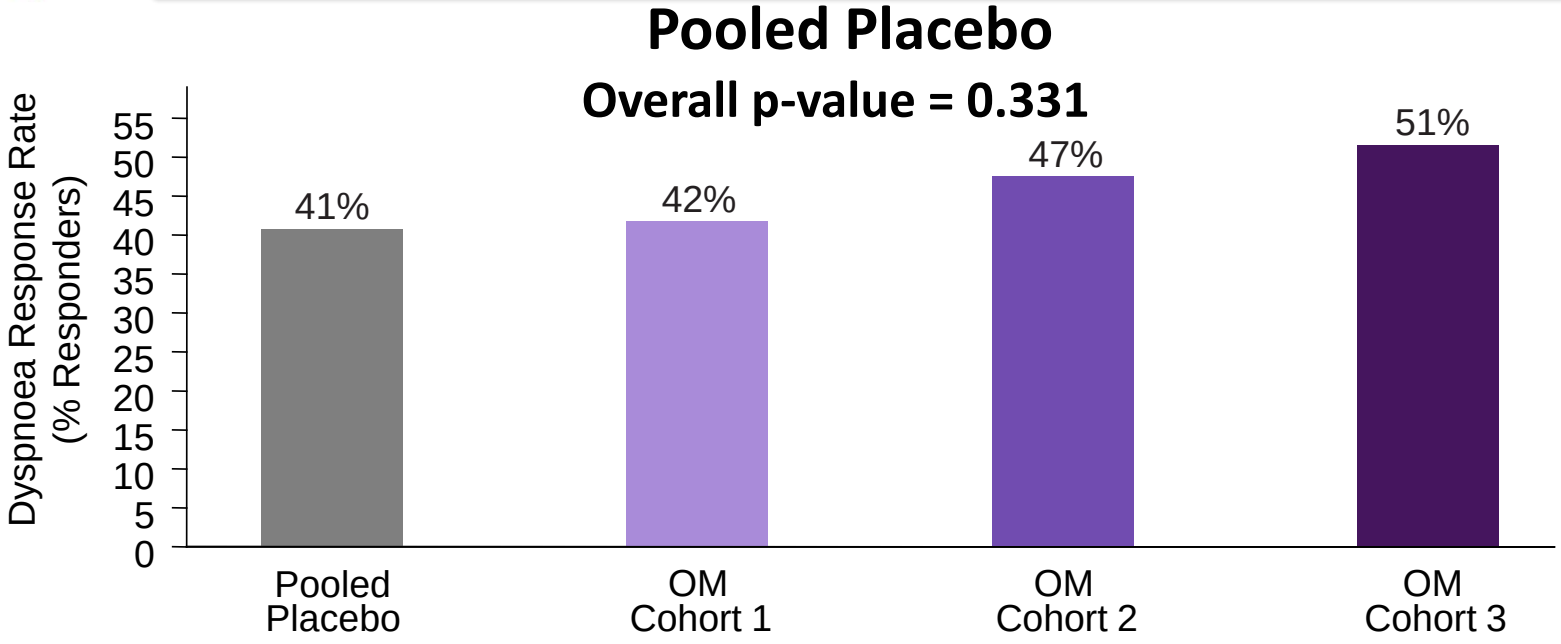
Study Design

Randomised, double-blind, placebo-controlled, sequential cohort study



* Randomisation within 24 hours of initial IV diuretic (Amendment 2)

Primary Efficacy Endpoint: Dyspnoea Response (Likert Scale)



Exploratory Analyses: Dose and Concentration Relationship

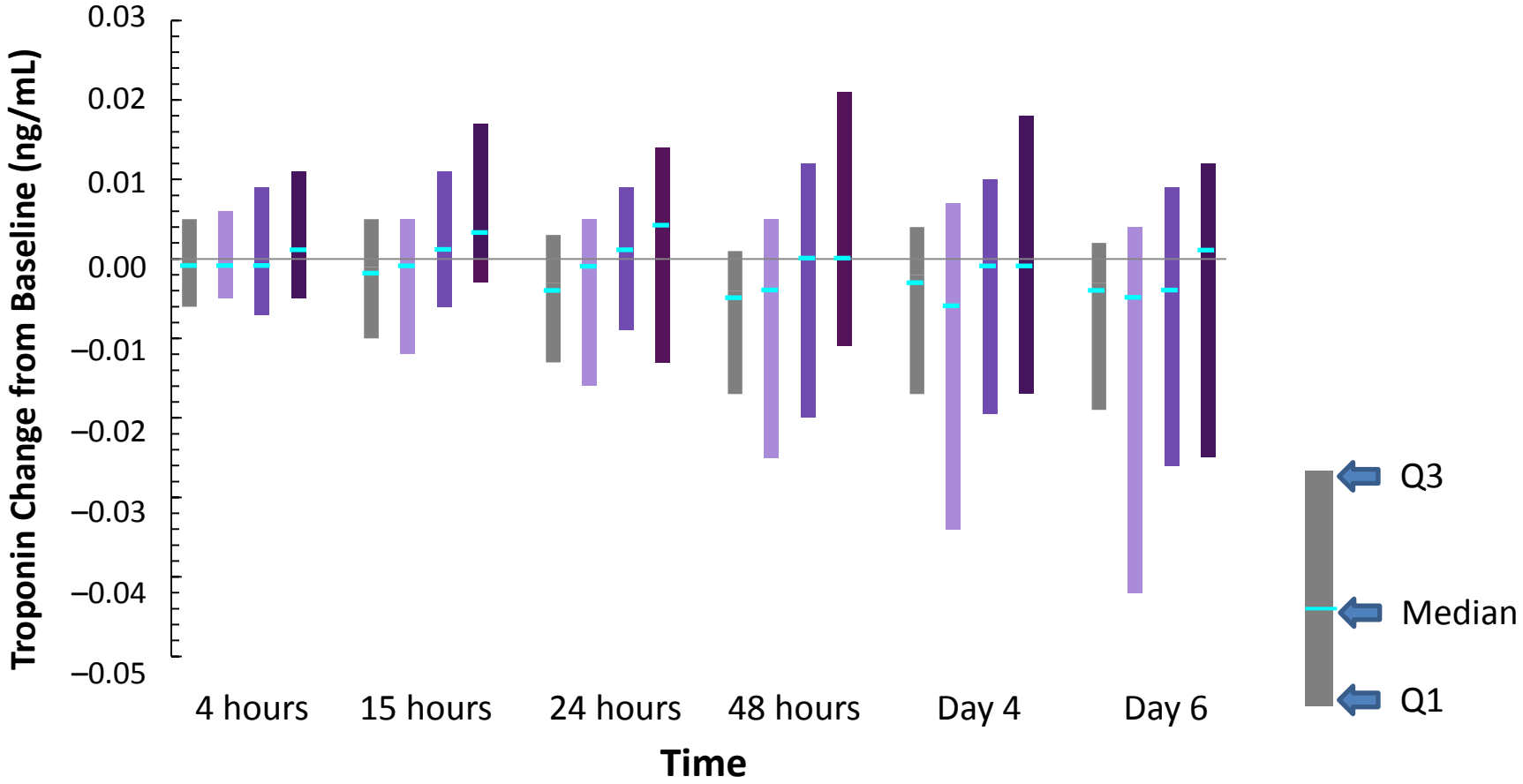
Dose & Concentration-Response	For Increases of…	Response Rate Ratio Increases…	95% CI	P-value
Dose*	50 mg total OM administered	5.5%	0.7% – 10.6%	0.025
Plasma concentration*	4000 hr*ng/mL AUC48h	6.4%	1.7% – 11.4%	0.007

Post-Randomization Adjudicated Events

Patient Incidence, n (%)	Pooled Placebo (N = 303)	Pooled OM (N = 303)	Cohort 1 OM (N = 103)	Cohort 2 OM (N = 99)	Cohort 3 OM (N = 101)
Death	**10 (3.3)**	**8 (2.6)**	**1 (1.0)**	**4 (4.0)**	**3 (3.0)**
Cardiovascular	10 (3.3)	8 (2.6)	1 (1.0)	4 (4.0)	3 (3.0)
ACS/MI (fatal)	0	1 (0.3)	0	0	1 (1.0)
All Rehospitalisations	**37 (12.2)**	**29 (9.6)**	**11 (10.7)**	**11 (11.1)**	**7 (6.9)**
Acute MI	1 (0.3)	1 (0.3)	1 (1.0)	0	0
Unstable angina	0	0	0	0	0
Heart failure	19 (6.3)	22 (7.3)	6 (5.8)	11 (11.1)	5 (5.0)
Other	18 (5.9)	7 (2.3)	4 (3.9)	0	3 (3.0)
All Index hospitalisation MI (non-fatal)	**2 (0.7)**	**5 (1.7)**	**1 (1.0)**	**0**	**4 (4.0)**
Investigator reported	0 (0.0)	2 (0.7)	0 (0.0)	0	2 (2.0)
Troponin triggered	2 (0.7)	3 (1.0)	1 (1.0)	0	2 (2.0)
Total MIs (Fatal + Rehosp + Nonfatal Index Hosp)	**3 (1.0)**	**7 (2.3)**	**2 (1.9)**	**0**	**5 (5.0)**

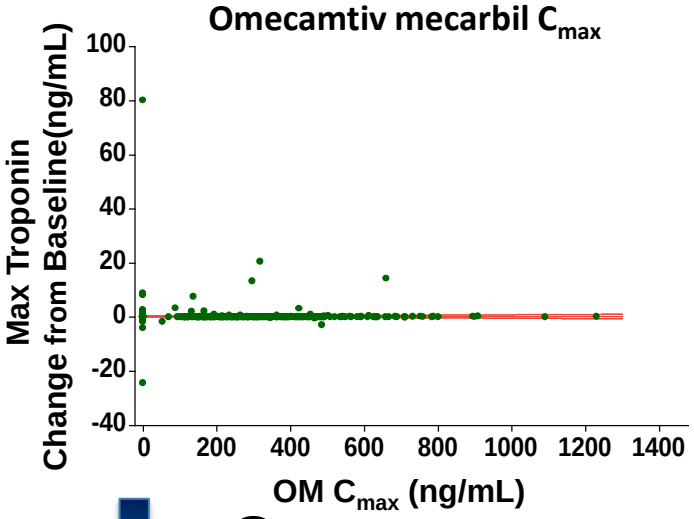
ACS/MI = Acute Coronary Syndrome/Myocardial Infarction. 66 patients had 73 positively adjudicated rehospitalisations.

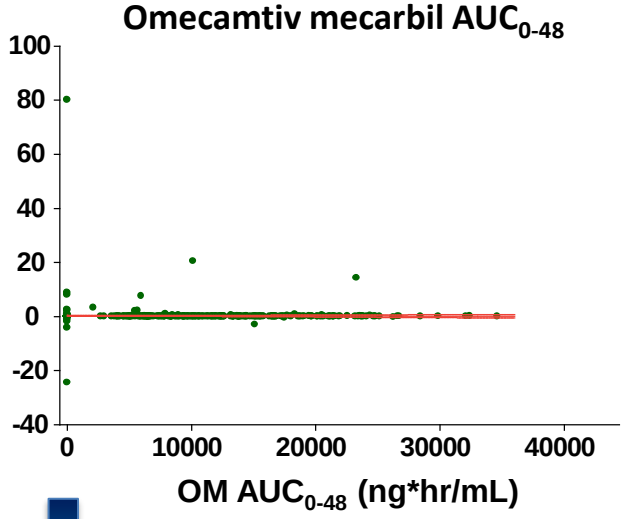
Troponin-I Change from Baseline (ng/mL) Compared with Pooled Placebo



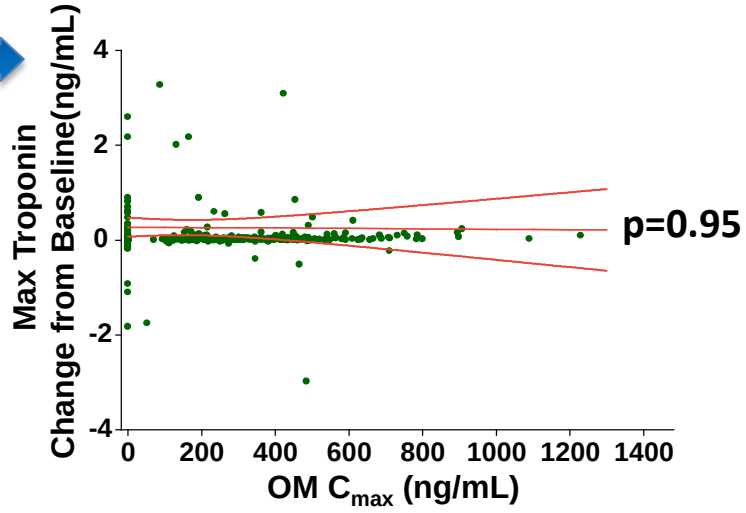
Baseline TnI (ng/mL)	Pooled Placebo	Cohort 1	Cohort 2	Cohort 3
Median	0.044	0.060	0.044	0.056
(Q1, Q3)	0.023, 0.080	0.028, 0.141	0.030, 0.084	0.026, 0.092

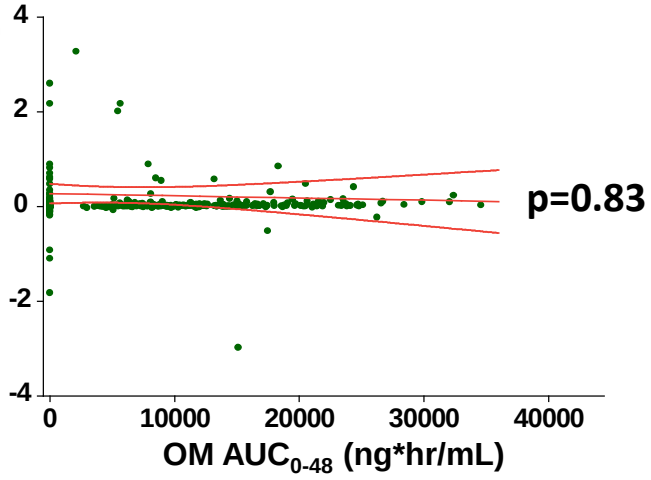
Omecamtiv Mecarbil Concentrations vs. Troponin-I Maximal Change from Baseline





Red lines represent linear regression line and its +/- SE. Baseline troponin-I is adjusted.





PK/PD Substudy Endpoint: Change in Systolic Ejection Time (SET)

PK Concentration Bin Analysis	Control	OM Concentration Bin 1	OM Concentration Bin 2	OM Concentration Bin 3
OM concentration range (ng/ml)		≥88-200	>200-300	>300-787
Change in SET (msec)				
N(n)	45 (88)	10 (18)	15 (23)	12 (19)
LS mean	-6.7	16.6	26.9	46.4
Difference from control		23.4	33.6	53.2
95% CI		(7.4, 39.4)	(19.8, 47.4)	(38.0, 68.3)
p-value		0.005	<0.0001	<0.0001
Linear regression slope	$p < 0.0001$			

Baseline systolic ejection time for all patients was 258 msec. N: number of patients in the bin, n: number of observations in the bin; Control = observations in Placebo + PK below quantification limit; PK bin concentration analysis: repeated measures analysis of covariance; Linear regression slope analysis: repeated measures multiple linear regression.

Summary

- Efficacy
  - OM did not meet the 1° endpoint of dyspnoea relief
  - Appeared to improve dyspnoea in Cohort 3
  - Trends towards reduction of worsening HF
- Safety
  - Overall SAE profile and tolerability similar to placebo
  - Increase in troponin; no clear relationship to OM concentration
  - Numerical imbalance in MIs in Cohort 3
  - No evidence of pro-arrhythmia
- Pharmacology
  - PK similar to healthy volunteers and stable HF patients
  - Systolic ejection time significantly increased consistent with MOA
  - Small fall in heart rate & rise in systolic BP at higher doses