

AN ANALYSIS OF THE RESPONSE TO CK-1827452, A SELECTIVE CARDIAC MYOSIN ACTIVATOR, IN STABLE HEART FAILURE PATIENTS STRATIFIED BY BASELINE CARDIAC FUNCTION

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INTRODUCTION

CK-1827452 (now known as *omecamtiv mecarbil*) is a cardiac myosin activator that increased indices of systolic function in a study of patients with stable heart failure (HF), CY 1121. Overall, at baseline, average stroke volume (SV) was normal (69 mL) in the study population, consistent with their compensated state. We stratified the population by baseline SV to see if the response to *omecamtiv mecarbil* was similar in the subgroup with diminished SV (≤ 50 mL).

OBJECTIVE

Evaluate the response to *omecamtiv mecarbil* in the patient sub-group with more severely depressed cardiac function as compared to those with more preserved cardiac function.

METHODS

This first Phase II trial of *omecamtiv mecarbil* was a multi-center, double-blind, randomized, placebo-controlled study in stable heart failure patients treated with an ACE inhibitor (or ARB) and a beta-blocker, \pm diuretics. In Cohorts 1-4, patients each received four treatments: three escalating doses of *omecamtiv mecarbil* and one placebo treatment which was randomized into the dosing sequence to maintain blinding. Each of the four treatments was at least one week apart. In Cohort 5, patients received two 72 hour treatments, *omecamtiv mecarbil* and placebo in a double-blind crossover fashion. The dosing scheme is shown below.

Dosing Table for Cohorts 1-5

	Loading Dose mg/kg/hr	Maintenance Dose mg/kg/hr	Entry EF and Cohort Features
Cohort 1 1 hr + 1hr n = 8	0.125 0.25 0.5	→ → → 0.0625 0.125 0.25	EF < 40% Echos at Baseline, 1.5, 24 hrs Four treatment sessions/patient
Cohort 2 1 hr + 1hr n = 9	0.5 0.75 1.0	→ → → 0.25 0.375 0.5	EF < 40% Echos at Baseline, 1.5, 24 hrs Four treatment sessions/patient
Cohort 3 1hr + 23hr n = 10	0.25 0.5 1.0	→ → → 0.025 0.05 0.1	EF < 40% Echos at Baseline, 1.5, 24, 48 hrs Four treatment sessions/patient
Cohort 4 1hr + 1hr + 22hr n = 8	0.25/0.125 0.5/0.25 1.0/0.5	→ → → 0.025 0.05 0.1	EF \leq 30% Echos at Baseline, 1.5, 24, 48 hrs Three women required Four treatment sessions/patient
Cohort 5 1hr + 1hr + 70hr n = 10	1.0/0.5 0.75/0.375	→ → 0.1 0.075	EF < 40% Echos at Baseline, 1.5, 24, 72, 96 hrs Two period crossover Dose reduction in last 2 patients

151 Total Treatment Periods Initiated

Abbreviations: systolic ejection time (SET), left ventricular out flow tract Doppler-derived stroke volume and cardiac output (LVOT SV, LVOT CO), fractional shortening (FS), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), ejection fraction by method of discs (EF_{MOD}), ejection fraction calculated by LVOT SV/LVEDV (EF_{HYBRID})

PATIENT POPULATION

Demographics and Baseline Characteristics

	Cohorts 1-5 (n=45)	
	Mean	(min-max)
Age (yrs)	58	30 – 77
Weight (kg)	78	52 – 115
Systolic BP (mmHg)	124	96 – 183
Diastolic BP (mmHg)	75	57 – 117
Heart Rate (bpm)	69	48 – 96
Ejection Fraction (%)	33	20 – 55

Cohorts 1-5

39 Men	6 Women
29 IHD	16 DCM

RESULTS

Echo PK/PD Relationship: Pooled Analysis

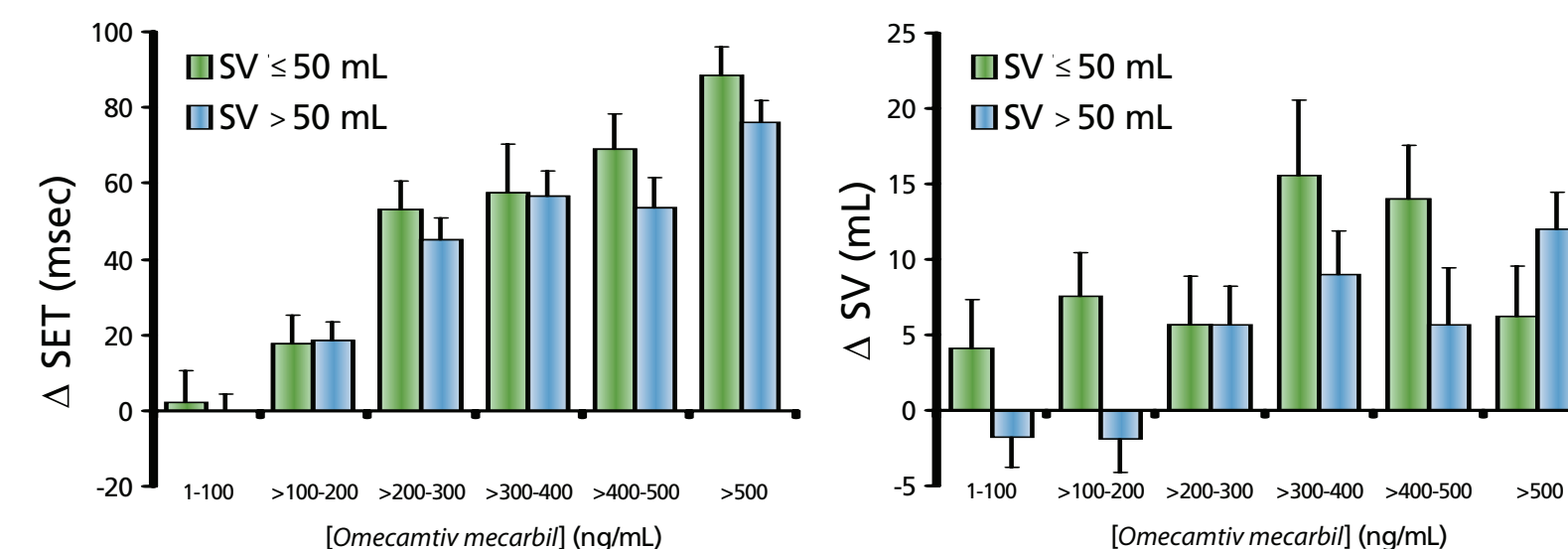
[Omecamtiv mecarbil] (ng/mL)	1-100	>100-200	>200-300	>300-400	>400-500	>500	Correlation versus [Omecamtiv mecarbil] (p value)	
Variable	Mean Baseline	Placebo Corrected Changes from Baseline Difference of Least Squares Means \pm SEM						
SET (msec)	316	1 \pm 4 NS	18 \pm 4 p < 0.0001	47 \pm 5 p < 0.0001	58 \pm 6 p < 0.0001	59 \pm 6 p < 0.0001	80 \pm 5 p < 0.0001	<0.0001
LVOT SV (mL)	69	0 \pm 2 NS	1 \pm 2 NS	5 \pm 2 p = 0.01	11 \pm 3 p < 0.0001	9 \pm 3 p < 0.0001	10 \pm 2 p < 0.0001	<0.0001
LVOT CO (mL/min)	4423	-32 \pm 116 NS	52 \pm 123 NS	180 \pm 141 NS	408 \pm 173 p = 0.02	400 \pm 189 p = 0.03	330 \pm 142 p = 0.02	0.0005
LVOTHR (bpm)	66	0 \pm 1 NS	0 \pm 1 NS	-2 \pm 1 p = 0.06	-4 \pm 2 p = 0.005	-2 \pm 2 NS	-4 \pm 1 p = 0.001	0.0003
EF _{MOD} (%)	33	0 \pm 1 NS	0 \pm 1 NS	1 \pm 1 NS	1 \pm 1 NS	0 \pm 1 NS	2 \pm 1 p = 0.02	0.009
EF _{HYBRID} (%)	32	0 \pm 1 NS	1 \pm 1 NS	3 \pm 2 p = 0.07	8 \pm 2 p < 0.0001	7 \pm 2 p = 0.0009	10 \pm 1 p < 0.0001	<0.0001
LVESV (mL)	168	1 \pm 4 NS	3 \pm 4 NS	-5 \pm 5 NS	-11 \pm 6 p = 0.06	-13 \pm 7 p = 0.06	-15 \pm 5 p = 0.003	<0.0001
LVEDV (mL)	243	1 \pm 5 NS	5 \pm 5 NS	-2 \pm 6 NS	-14 \pm 8 p = 0.07	-15 \pm 8 p = 0.07	-16 \pm 6 p = 0.01	0.0005

Echocardiograms from all Timepoints Cohorts 1, 2, 3, 4, & 5 Combined n = 564 echocardiograms

p < 0.05

EF_{HYBRID} = LVOT SV (by Doppler) / LVEDV

Echo PK/PD Relationship: Stratification by Baseline Stroke Volume



Response in patients with depressed stroke volumes at baseline is generally greater than response in patients with adequate stroke volumes at baseline

Placebo corrected changes from baseline LSM \pm SEM

Echo PK/PD Relationship: Stratification by Baseline Stroke Volume

[Omecamtiv mecarbil] (ng/mL)	1-100	>100-200	>200-300	>300-400	>400-500	>500
Variable	Baseline	Placebo Corrected Changes from Baseline Difference of Least Squares Means \pm SEM				
SET (msec)	2 \pm 8 NS	18 \pm 7 p = 0.017	53 \pm 8 p < 0.0001	58 \pm 13 p < 0.0001	69 \pm 9 p < 0.0001	88 \pm 8 p < 0.0001
LVOT SV (mL)	4 \pm 3 NS	8 \pm 3 p = 0.01	6 \pm 3 p = 0.08	16 \pm 5 p = 0.002	14 \pm 4 p = 0.0002	6 \pm 3 p = 0.06
FS (%)	2 \pm 2 NS	3 \pm 1 p = 0.07	2 \pm 2 NS	6 \pm 2 p = 0.01	4 \pm 2 p = 0.02	5 \pm 2 p = 0.0007
SET (ms)	0 \pm 4 NS	19 \pm 5 p = 0.0002	45 \pm 6 p < 0.0001	57 \pm 7 p < 0.0001	53 \pm 8 p < 0.0001	76 \pm 6 p < 0.0001
LVOT SV (mL)	-2 \pm 2 NS	-2 \pm 2 NS	6 \pm 3 p = 0.03	9 \pm 3 p = 0.002	6 \pm 4 NS	12 \pm 3 p < 0.0001
FS (%)	0 \pm 1 NS	1 \pm 1 NS	3 \pm 1 p = 0.0007	2 \pm 1 NS	1 \pm 2 NS	4 \pm 1 p < 0.0001

Echocardiograms from all Timepoints; Cohorts 1, 2, 3, 4, & 5 Combined

p < 0.05

Echo PK/PD Relationship: Stratification by Baseline Ejection Fraction

[Omecamtiv mecarbil] (ng/mL)	1-100	>100-200	>200-300	>300-400	>400-500	>500
Variable	Baseline	Placebo Corrected Changes from Baseline Least Squares Mean \pm SEM				
SET (msec)	4 \pm 6 NS	17 \pm 6 p = 0.009	48 \pm 8 p < 0.0001	52 \pm 8 p < 0.0001	60 \pm 9 p < 0.0001	88 \pm 7 p < 0.0001
LVOT SV (mL)	-1 \pm 3 NS	2 \pm 3 NS	1 \pm 3 NS	12 \pm 4 p = 0.0009	9 \pm 4 p = 0.03	9 \pm 3 p = 0.004
FS (%)	0 \pm 1 NS	1 \pm 1 NS	1 \pm 1 NS	3 \pm 1 p = 0.003	2 \pm 1 NS	4 \pm 1 p < 0.0001
SET (ms)	-1 \pm 5 NS	21 \pm 6 p = 0.0002	47 \pm 6 p < 0.0001	67 \pm 8 p < 0.0001	61 \pm 9 p < 0.0001	73 \pm 6 p < 0.0001
LVOT SV (mL)	1 \pm 2 NS	0 \pm 2 NS	7 \pm 3 p = 0.008	9 \pm 4 p = 0.02	8 \pm 4 p = 0.04	9 \pm 3 p = 0.002
FS (%)	1 \pm 1 NS	2 \pm 1 NS	4 \pm 1 p = 0.0004	1 \pm 2 NS	2.4 \pm 2 NS	5 \pm 1 p = 0.0002

Echocardiograms from all Timepoints; Cohorts 1, 2, 3, 4, & 5 Combined

p < 0.05

PK/PD Summary

- At >100 ng/mL
 - Systolic ejection time (SET) is increased
 - Fractional shortening (FS) is increased
- At >200 ng/mL
 - Doppler-derived stroke volume (LVOT SV) is increased
 - Heart rate starts to decrease as stroke volume goes up
- At > 300 ng/mL
 - Doppler-derived cardiac output (LVOT CO) is increased
 - EF_{HYBRID} is increased
 - LV end systolic and diastolic volumes (LVESV, LVEDV) start to decrease, possibly due to unloading of the ventricle
- At > 400 ng/mL
 - Increases in stroke volume and cardiac output plateau
- Generally greater response observed in patients with reduced vs. adequate baseline stroke volumes

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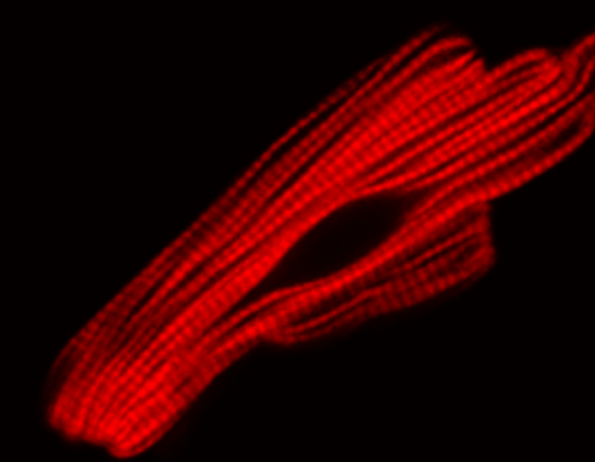
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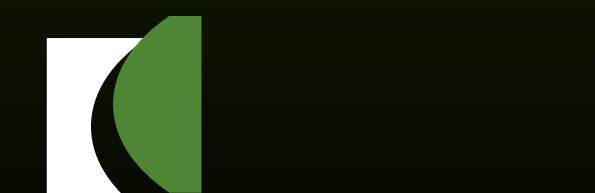
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1 Malik FI, Saikali KG, Clarke CP, Teerlink JR, Wolff AA. Systolic Ejection Time is a Sensitive Indicator of Left Ventricular Systolic Function During Treatment with the Selective Cardiac Myosin Activator, CK-1827452. 2007 Annual Heart Failure Society of America Meeting, Washington, DC. September, 2007.



CONCLUSIONS

- Omecamtiv mecarbil* increases systolic ejection time, stroke volume, cardiac output, fractional shortening, and ejection fraction (by either method) in a concentration-dependent manner.
- Omecamtiv mecarbil* increased indices of cardiac function in patients with more severely depressed cardiac function to a similar or greater extent as compared to the entire population.
- These findings support further study in a larger patient population, and translation of this novel and unique mechanism into populations with acute and chronic heart failure.



CYTOKINETICS