The Selective Cardiac Myosin Activator, CK-1827452, Increases Systolic Function in a Concentration-Dependent Manner in Patients with Stable Heart Failure

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Introduction

CK-1827452 (CK-452) is a small molecule designed to improve cardiac function by the novel mechanism of directly activating cardiac myosin. In healthy subjects CK-452 increases systolic ejection time (SET), stroke volume (SV), fractional shortening (FS), and ejection fraction (EF)[1].

This multi-center, double-blind, placebo controlled trial sought to assess the effects of CK-452 in patients with stable heart failure.

Objectives

- Evaluate the safety and tolerability of CK-452 administered as an intravenous infusion to stable heart failure patients
- Establish a relationship between plasma concentration and pharmacodynamic effect for CK-452
- Determine the pharmacokinetics of CK-452 in stable heart failure patients

Methods

This first Phase II trial of CK-452 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, ± diuretics. In Cohorts 1-4, patients each received four treatments: three escalating doses of CK-452 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, CK-452 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 ≤ 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	→ or →	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

[CK-1827452] (ng/mL)		1-100	>100-200	>200-300	>300-400	>400-500	>500	Correlation versus [CK-1827452] (p value)
Variable	Mean Baseline	Placebo Corrected Changes from Baseline Difference of Least Squares Means ± SEM						
SET (msec)	316	1 ± 4 NS	18 ± 4 p < 0.0001	47 ± 5 p < 0.0001	58 ± 6 p < 0.0001	59 ± 6 p < 0.0001	80 ± 5 p < 0.0001	<0.0001
LVOT SV (mL)	69	0 ± 2 NS	1 ± 2 NS	5 ± 2 p = 0.01	11 ± 3 p < 0.0001	9 ± 3 p = 0.001	10 ± 2 p < 0.0001	<0.0001
LVOT CO (L/min)	4423	-32 ± 116 NS	52 ± 123 NS	180 ± 141 NS	408 ± 173 p = 0.02	400 ± 189 p = 0.03	330 ± 142 p = 0.02	0.0005
HR (bpm)	66	0 ± 1 NS	0 ± 1 NS	-2 ± 1 p = 0.06	-4 ± 2 p = 0.005	-2 ± 2 NS	-4 ± 1 p = 0.001	0.0003

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

p < 0.05

Echo PK/PD Relationship: Pooled Analysis

[CK-1827452] (ng/mL)		1-100	>100-200	>200-300	>300-400	>400-500	>500	Correlation versus [CK-1827452] (p value)
Variable	Mean Baseline	Placebo Corrected Changes from Baseline Difference of Least Squares Means ± SEM						
FS (%)	18	1 ± 1 NS	1 ± 1 p = 0.04	3 ± 1 p = 0.0004	3 ± 1 p = 0.009	2 ± 1 p = 0.03	5 ± 1 p < 0.0001	<0.0001
EF_{MOD} (%)	33	0 ± 1 NS	0 ± 1 NS	1 ± 1 NS	1 ± 1 NS	0 ± 1 NS	2 ± 1 p = 0.02	0.009
EF_{HYBRID} (%)	32	0 ± 1 NS	1 ± 1 NS	3 ± 2 P = 0.07	8 ± 2 p < 0.0001	7 ± 2 p = 0.0009	10 ± 1 p < 0.0001	<0.0001
LVESV (mL)	168	1 ± 4 NS	3 ± 4 NS	-5 ± 5 NS	-11 ± 6 p = 0.08	-13 ± 7 p = 0.06	-15 ± 5 p = 0.003	<0.0001
LVEDV (mL)	243	1 ± 5 NS	5 ± 5 NS	-2 ± 6 NS	-14 ± 8 p = 0.07	-15 ± 8 p = 0.07	-16 ± 6 p = 0.01	0.0005

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

p < 0.05

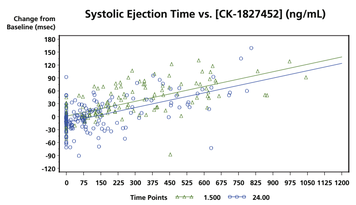
EF_{HYBRID} = LVOT SV (by Doppler) / LVEDV

Echo PK/PD Relationship: Cohort 5

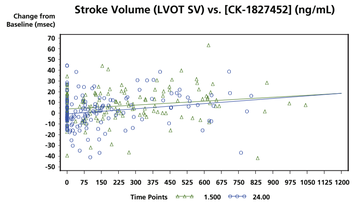
Nominal Time Point (hr)		1.5	24	72	96
CK-1827452 Infusion		On	On	On	Off
Arithmetic Mean [CK-1827452] (ng/mL) (n=8; min, max)		660 (249, 1044)	594 (312, 806)	803 (487, 1293)	388 (213, 762)
Variable	Baseline	Placebo Corrected Changes from Baseline Least Squares Mean ± SEM (n on CK-1827452, n on placebo)			
SET (msec)	340	60 ± 30 (7, 8) p = 0.08	37 ± 43 (7, 7) NS	11 ± 23 (6, 7) NS	34 ± 4 (6, 7) p = 0.003
LVOT SV (mL)	73	9 ± 8 (7, 8) NS	2 ± 12 (7, 7) NS	-2 ± 8 (6, 7) NS	-1 ± 9 (6, 7) NS
LVOT HR (bpm)	72	-6 ± 8 (7, 7) NS	-3 ± 8 (8, 7) NS	2 ± 3 (7, 7) NS	-3 ± 5 (7, 7) NS
LVESV (mL)	142	-22 ± 13 (8, 8) NS	-17 ± 18 (8, 8) NS	-33 ± 8 (7, 7) p = 0.01	2 ± 16 (7, 7) NS
LVEDV (mL)	211	-30 ± 15 (8, 8) p = 0.08	-23 ± 21 (8, 8) NS	-42 ± 16 (7, 7) p = 0.053	2 ± 22 (7, 7) NS

p < 0.05

Echo PK/PD Relationship: Concentration Response Similar at 1.5 and 24 hr



Cohorts 1, 2, 3, 4, and 5 at times 1.5 and 24 hours
Echo timepoints common to all cohorts



Cohorts 1, 2, 3, 4, and 5 at times 1.5 and 24 hours
Echo timepoints common to all cohorts

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
- CK-452 mediated changes in cardiac function appear persistent over 24 hours
- With 72 hr infusion, decreases in ventricular volumes appear sustained while other parameters may return to baseline as a consequence of homeostatic compensation but with the heart now at a new set point in terms of ventricular volumes

Safety

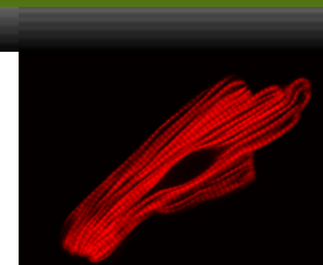
- Three SAEs (only one deemed related to CK-452)
  - Non ST elevation MI in patient with a drug overdose
  - Septicemia in setting of diabetic foot ulcer
  - Pneumonia
- For patients tolerant of all study drug infusions, no consistent pattern of adverse events with either dose or duration of infusion emerged

Incidence of Treatment-Emergent Adverse Events Occurring in 2 or More Patients

			First Hour Loading Dose (mg/kg/hr)						
			Placebo	0.125	0.25	0.5	0.75	1.0	2.2
	Overall All Patients (N = 45)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	n = 16 n = 17 n = 8	n = 8	n = 9 n = 18	n = 16 n = 18	n = 8 n = 2	n = 6 n = 16 n = 8	n = 1
Orthostatic hypotension	4 (8.9%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	1 (6.3%) 1 (5.9%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 1 (50.0%)	1 (16.7%) 0 (0.0%) 0 (0.0%)	0 (0.0%)
Constipation	3 (6.7%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	0 (0.0%) 1 (5.9%) 1 (12.5%)	0 (0.0%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)
Somnolence	3 (6.7%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	0 (0.0%) 1 (5.9%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 1 (6.3%) 0 (0.0%)	0 (0.0%)
Troponin increased	3 (6.7%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 2 (20%)	1 (100%)
Dizziness postural	2 (4.4%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 0 (0.0%)	1 (16.7%) 0 (0.0%) 0 (0.0%)	0 (0.0%)
Dyspnea	2 (4.4%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	1 (6.3%) 0 (0.0%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)
Headache	2 (4.4%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	1 (6.3%) 0 (0.0%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)
Hypotension	2 (4.4%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	1 (16.7%) 0 (0.0%) 0 (0.0%)	0 (0.0%)
Infusion site pain	2 (4.4%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	0 (0.0%) 0 (0.0%) 1 (12.5%)	0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 1 (5.6%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)
Musculoskeletal pain	2 (4.4%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort5	0 (0.0%) 0 (0.0%) 1 (12.5%)	1 (12.5%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)
Sinus bradycardia	2 (4.4%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	1 (16.7%) 0 (0.0%) 1 (12.5%)	0 (0.0%)
Urinary tract infection	2 (4.4%)	Cohorts 1 &/or 2 Cohorts 3 & 4 Cohort 5	1 (6.3%) 0 (0.0%) 0 (0.0%)	0 (0.0%)	0 (0.0%) 0 (0.0%)	1 (6.3%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	0 (0.0%) 0 (0.0%) 0 (0.0%)	0 (0.0%)

An adverse event was counted once in each treatment period per patient and only once per patient overall.
Percentages are calculated as 100 x (n/N).

- Five patients were discontinued on study drug
  - Two syndromes of clinical intolerance due to excessive [CK-452]
    - Drug overdose leading to [CK-452] ~1700 ng/mL; troponin increased
    - At highest dose level, female with high body weight (high total dose administered given weight based dosing) and low clearance achieved [CK-452] ~1350 ng/mL; troponin increased
  - Asymptomatic troponin I increase in hypertensive patient (baseline 182/116) discovered following completion of infusion
  - Local contractile dysfunction noted on echocardiogram; peer review of echocardiograms did not confirm finding
  - QTc > 500 msec during infusion; core lab determined QTcF 493 msec at baseline, 499 msec at termination



Conclusions

1. CK-452 increases systolic ejection time, stroke volume, cardiac output, fractional shortening, and ejection fraction (by either method) in a concentration-dependent manner
2. CK-452 decreases left ventricular end systolic and end diastolic volumes in a concentration-dependent manner, which may be a consequence of decreases in filling pressures that could result in reverse remodeling with chronic dosing
3. CK-452 appears to be generally well tolerated in stable HF patients over a broad range of plasma concentrations during continuous intravenous administration
4. These findings support further study in a larger patient population, and translation of this novel and unique mechanism into populations with more severe, and acute heart failure

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References

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.

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