First Clinical Trial of the Selective Cardiac Myosin Activator, CK-1827452, in Heart Failure: Effect of Dose and Plasma Concentration on Systolic Function

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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 a dog model of heart failure, intravenous infusion of CK-452 increased left ventricular systolic function and cardiac output, with attendant decreases in filling pressures and heart rate.[1,2] Importantly, these effects on cardiac function did not result in an increase in coronary blood flow or myocardial oxygen demand. As opposed to ß-adrenergic receptor agonists and phosphodiesterase inhibitors, which increase the rate of pressure development (dP/dt) and shorten left ventricular systolic ejection time, CK-452 increased systolic function by increasing systolic ejection time without changing dP/dt.

In a Phase I trial in healthy volunteers, the most sensitive indicator of pharmacologic effect was a concentration-dependent increase in systolic ejection time (SET) accompanied by increases in ejection fraction (EF).[3] This trial sought to assess the effects of CK-452 in patients with stable heart failure.

Objectives

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

Dosing Table for Cohorts 1-3:

	Loading Dose	Maintenance Dose	Predicted C_{max} (median)	Measured C_{max} (median)
	mg/kg/hr	mg/kg/hr	ng/mL	ng/mL
Cohort 1 1hr + 1hr	0.125	0.0625	90	93
	0.25	0.125	175	177
	0.5	0.25	320	331
Cohort 2 1hr + 1hr	0.5	0.25	320	331
	0.75	0.375	500	578
	1.0	0.5	650	613
Cohort 3 1hr + 23hr	0.25	0.025	175	183
	0.5	0.05	320	271
	1.0	0.1	650	600

Methods

This first Phase II trial of CK-452 is a multi-center, double-blind, randomized, placebo-controlled study in patients with EF < 40% and treated with an ACE inhibitor (or ARB) and a beta-blocker, ± diuretics. Cohorts of 8 completed patients each receive 3 infusions of escalating doses of CK-452 and 1 placebo treatment, which is randomized into the sequence to maintain blinding. Each of the four infusions are at least 1 week apart. Duration of infusion was 2 hours in Cohorts 1 and 2, and 24 hours in Cohort 3.

Results

In an analysis of data from Cohorts 1 and 2, and data from a pre-specified interim analysis for Cohort 3 (n = 6), echocardiographic data were paired with coincident measured plasma concentrations of CK-452 to perform a pharmacokinetic/pharmacodynamic analysis.

Placebo Corrected Changes from Baseline

[CK-452] ng/mL)		1-100	>100-200	>200-300	>300-400	>400-500	>500-817
Observations (n)		58	36	21	14	8	12
	Baseline						
SET (ms)[1]	320	2 ± 5	20 ± 5†	49 ± 7&	61 ± 8&	65 ± 10&	95 ± 9&
SV (mL)[1]	71	0 ± 2	-2 ± 2	4 ± 3	10 ± 3*	10 ± 4#	22 ± 4&
FS (%)[2]	17	1 ± 1	1 ± 1	3 ± 1#	3 ± 1	1 ± 2	4 ± 2#
EF (%)[3]	34	0 ± 1	0 ± 1	1 ± 1	2 ± 2	0 ± 2	2 ± 2
HR (bpm)	60	0 ± 1	0 ± 1	0 ± 2	-2 ± 2	0 ± 2	-5 ± 2*

Least Squares Mean ±SEM # $p < 0.05$ * $p \le 0.01$ † $p < 0.001$ & $p < 0.0001$
[1] Doppler-derived parameters [2] M-mode [3] Biplane MOD

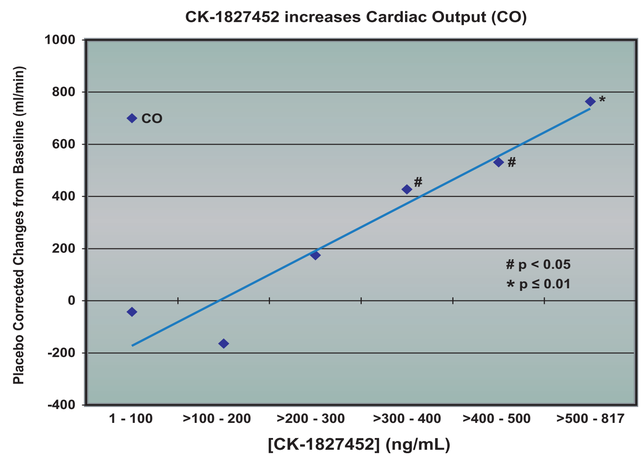
There were statistically significant correlations between concentration and increases in SET, Stroke Volume (SV) (each $p < 0.0001$), Fractional Shortening (FS) and Cardiac Output (CO) ($p < 0.01$). Changes in EF did not achieve statistical significance. Heart rate declined slightly at the higher concentrations and there were no dose-related changes in blood pressure. Treatments were well tolerated at pre-specified dosages.

Results (contd.)

Placebo Corrected Changes from Baseline

[CK-452] ng/mL)		1-100	>100-200	>200-300	>300-400	>400-500	>500-817
Observations (n)		58	36	21	14	8	12
	Baseline						
LVESV (ml)[3]	165	-3 ± 5	0 ± 6	-1 ± 7	-11 ± 8	-10 ± 10	-3 ± 9
LVEDV (ml)[3]	244	-5 ± 7	2 ± 7	4 ± 9	-13 ± 10	-12 ± 13	0 ± 11
IVRT (ms)[1]	92	2 ± 4	9 ± 5	21 ± 6†	22 ± 7*	8 ± 9	28 ± 7†
IVCT (ms)[1]	90	3 ± 4	1 ± 5	5 ± 7	1 ± 7	-4 ± 11	-6 ± 9
E/A[1]	1.2	-0.2 ± 0.1*	-0.2 ± 0.1†	-0.3 ± 0.1&	-0.4 ± 0.1&	-0.2 ± 0.1	-0.4 ± 0.1&
Peak E (m/sec)[1]	71	-3 ± 2	-4 ± 2	-7 ± 3#	-4 ± 3	2 ± 4	-3 ± 4
Peak A (m/sec)[1]	70	3 ± 2	6 ± 2*	13 ± 3&	15 ± 3&	13 ± 4*	14 ± 3&
MVDT (ms)[1]	206	-1 ± 9	7 ± 10	-5 ± 12	16 ± 14	-13 ± 17	31 ± 15#

Least Squares Mean ±SEM # $p < 0.05$ * $p \le 0.01$ † $p < 0.001$ & $p < 0.0001$
[1] Doppler-derived parameters [3] Biplane MOD



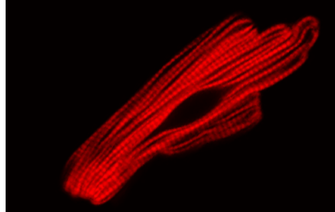
Changes in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were not statistically significant. Isovolumic relaxation time (IVRT) increased at higher concentrations. There was no change in isovolumic contraction time (IVCT). The ratio of early to late mitral filling (E/A) decreased, largely due to an increase in the atrial component of diastolic filling. Mitral valve deceleration time (MVDT) did not show consistent changes.

References

1 Malik F, et al. Direct Activation of Cardiac Myosin by CK-1827452 Improves Cardiac Function in a Dog Heart Failure Model. Journal of Cardiac Failure August 2005 (Vol. 11, Issue 6 (Supplement), Page S95).

2 Shen YT, et al. Activating Cardiac Myosin, a Novel Inotropic Mechanism To Improve Cardiac Function in Conscious Dogs with Congestive Heart Failure. Journal of Cardiac Failure August 2006 (Vol. 12, Issue 6 (Supplement), Page S87).

3 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

- CK-452 increases stroke volume, cardiac output, fractional shortening, and systolic ejection time in a concentration-dependent manner
- CK-452 appears to be well tolerated in stable HF patients over a broad range of plasma concentrations during continuous intravenous administration
- The observed improvements in systolic function 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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