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Systolic Ejection Time is a Sensitive Indicator of Left Ventricular Systolic Function During Treatment with the Selective Cardiac Myosin Activator, CK-1827452

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Introduction

The selective cardiac myosin activator, CK-1827452, was developed to address the liabilities of current inotropic mechanisms for the treatment of acute and chronic heart failure. In a dog model of heart failure, intravenous infusion of CK-1827452 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-1827452 increased systolic function by increasing systolic ejection time without changing dP/dt. The mechanism of action is predicted to impact minimally cardiac oxygen consumption and thus potentially to improve myocardial efficiency and function simultaneously. This pharmacologic profile is unique among agents that improve cardiac function and could be of benefit to patients with heart failure.

In the first in humans study, a 6-hr infusion of CK-1827452 was given to healthy men. As previously reported[3], CK-1827452 produced dose-dependent and statistically significant increases in ejection fraction (EF) and fractional shortening (FS) at 6 hrs as compared to placebo. As seen preclinically, underlying these increases was a dose-dependent lengthening of the systolic ejection time (SET). We have now performed an analysis of these indices of systolic function using the echocardiographic data and CK-1827452 plasma concentrations at all measured timepoints during the study.

Objectives

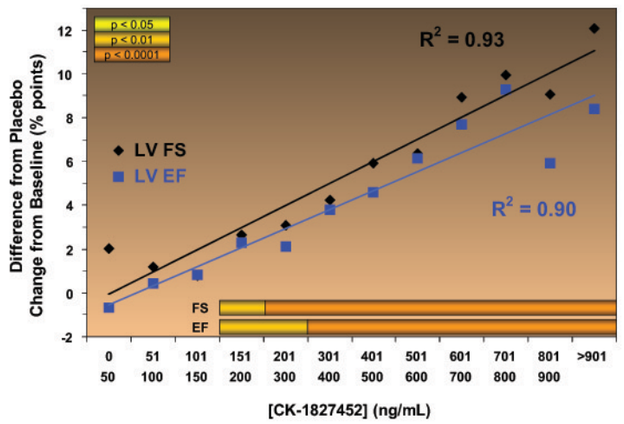
- **Evaluate the concentration-response relationship of the cardiac myosin activator, CK-1827452, on left ventricular function in healthy volunteers**
- **Confirm that underlying the increases in fractional shortening and ejection fraction is a concentration-dependent increase in the systolic ejection time as was seen preclinically**

References

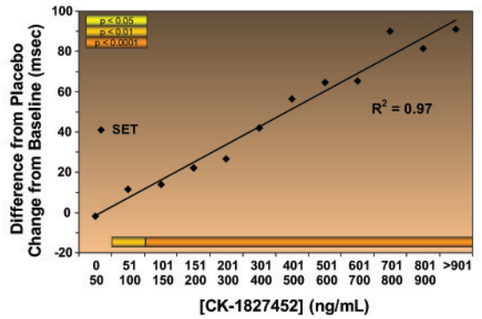
1. Malik F, *et al.* Direct Activation of Cardiac Myosin by CK-1827452 Improves Cardiac Function in a Dog Heart Failure Model. *Journal of Cardiac Failure* August 2005 (Vol. 11, Issue 6 (Supplement), Page S95).
2. Shen YT, *et al.* Activating Cardiac Myosin, a Novel Inotropic Mechanism To Improve Cardiac Function in Conscious Dogs with Congestive Heart Failure. *Journal of Cardiac Failure* August 2006 (Vol. 12, Issue 6 (Supplement), Page S87)
3. Teerlink JR, *et al.* The Selective Cardiac Myosin Activator, CK-1827452, Increases Left Ventricular Systolic Function by Increasing Ejection Time: Results of a First-in-Human Study of a Unique and Novel Mechanism. *Journal of Cardiac Failure* December 2006 (Vol. 12, Issue 9, Page 763)

Results

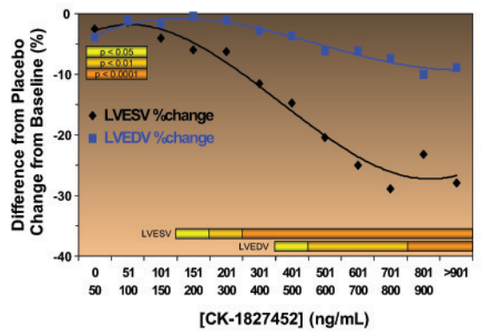
CK-1827452 increases EF and FS in a concentration-dependent manner



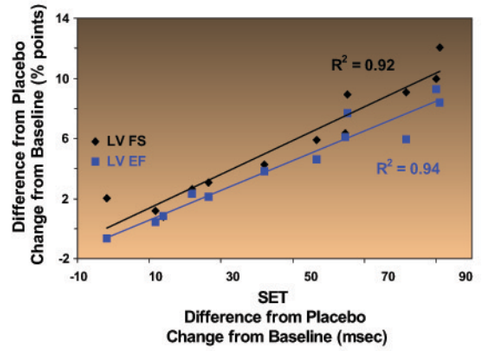
CK-1827452 lengthens SET in a concentration-dependent manner



CK-1827452 decreases LVESV in a concentration-dependent manner with smaller effects relative to baseline for LVEDV



Increases in EF and FS are well correlated with increases in SET



Methods

Healthy men (n=34 subjects) received a 6-hr double blind infusion each week x 4. Each subject received 3 ascending CK-1827452 doses with a placebo infusion randomized into the treatment sequence. CK-1827452 was studied at 10 dose rates ranging from 0.005 to 1 mg/kg/hr. Echocardiograms obtained at baseline, 1, 3, 6, 7, 8, 10, and 24 hrs were measured blinded to treatment. Echocardiographic variables were paired with coincident measured plasma concentrations of CK-1827452. A total of 484 observations comprised the analysis dataset. The data were binned in 50 to 100 ng/mL increments and the least squares mean difference for the change from baseline as compared to placebo was computed for each bin.

Dose Escalation

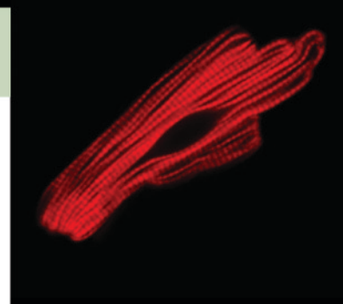
	Dose (mg/kg/hr)									
	0.005 (n=6)	0.015 (n=6)	0.025 (n=12)	0.0625 (n=6)	0.125 (n=14)	0.25 (n=8)	0.5 (n=16)	0.625 (n=5)	0.75 (n=2)	1.0 (n=2)
Cohort 1*	X	X	X							
Cohort 2*			X	X	X					
Cohort 3*					X	X	X			
Cohort 4*							X	X	X	X

* A placebo infusion is randomized into each subject's treatment sequence.
Simultaneous echocardiogram and PK timepoints at -1, 1, 3, 6, 7, 8,10, and 24 hours after infusion start

The Maximum Tolerated Dose (MTD) is 0.5 mg/kg/hr X 6 hrs
Mean C_{max} = 905 ng/mL; Range = 497-1242 ng/mL

Not tolerated | Well tolerated; too few subjects to define MTD

	Baseline Value	Least Squares Mean Differences in Change from Baseline as Compared to Placebo											
SET (msec)	308	-1.8	11.7	14.1	22.0	26.5	42.1	56.6	64.7	65.3	90.0	81.6	91.0
LV FS (% points)	35.2	2.0	1.2	0.8	2.6	3.1	4.2	5.9	6.4	8.9	10.0	9.1	12.1
LV EF (% points)	61.8	-0.7	0.4	0.8	2.3	2.1	3.8	4.6	6.1	7.7	9.3	5.9	8.4
LV ESV (mL)	46	-1.1	-0.6	-1.8	-2.8	-2.9	-5.3	-6.8	-9.4	-11.5	-13.3	-10.7	-12.8
LV EDV (mL)	120	-4.7	-1.3	-2.2	-0.5	-1.4	-3.3	-4.3	-7.3	-7.3	-8.8	-12.1	-10.6
		0 50	51 100	101 150	151 200	201 300	301 400	401 500	501 600	601 700	701 800	801 900	>901
		[CK-1827452] (ng/mL)											
		p > 0.05				p < 0.05		p < 0.01		p < 0.0001			



Conclusions

In this first in man study:

1) CK-1827452 significantly increased LV EF and LV FS over a range of well tolerated plasma concentrations.
2) Systolic ejection time was the most sensitive marker of drug effect.
3) Increases in EF and FS were well correlated with SET.
4) Easily measured, SET may be a useful indicator of drug effect in patients with heart failure.

CYTOKINETICS