Rationale and Design for a Phase II Study Evaluating the Effect of the Cardiac Myosin Activator, CK-1827452, on Cardiac Function, Hemodynamics, and Myocardial Oxygen Consumption in Patients with Heart Failure

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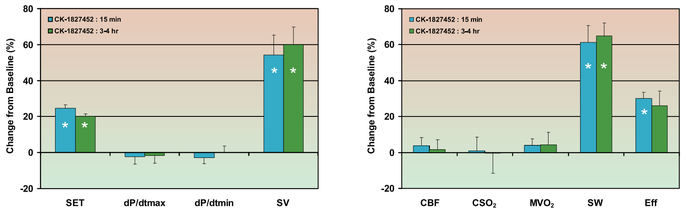
Introduction and Rationale

CK-1827452 increases systolic function by the novel mechanism of directly activating cardiac myosin. In dogs with heart failure, CK-1827452 increased systolic function by increasing systolic ejection time (SET) without changing dP/dt or myocardial oxygen consumption, thus increasing myocardial efficiency. This finding is in contrast to clinically available inotropic agents such as beta-adrenergic receptor agonists and phosphodiesterase inhibitors, which increase dP/dt, shorten SET, and increase oxygen consumption.

Pacing Induced Dog Heart Failure Model[1]

CK-1827452 (0.5 mg/kg bolus + 0.5 mg/kg/hr infusion)

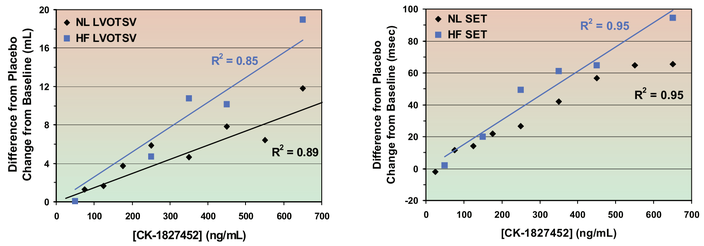


SET = Systolic Ejection Time; SV = Stroke Volume; CBF = Coronary Blood Flow; CSO_2 = Coronary Sinus O_2 content, MVO_2 = Myocardial Oxygen Consumption; SW = Stroke Work; Eff = Cardiac Efficiency

Using echocardiography in healthy volunteers[2] and stable heart failure[3] patients, we have demonstrated that in a concentration dependent manner, CK-1827452 increases Doppler derived stroke volume by the underlying mechanism of increasing the systolic ejection time as was found preclinically.

Healthy Volunteers[2] and Patients with Stable Heart Failure[3]

Pharmacokinetic/Pharmacodynamic Relationship



NL = Healthy Volunteers; HF = Stable Heart Failure Patients
LVOTSV = Left Ventricular Outflow Tract Stroke Volume; SET = Systolic Ejection Time

In this Phase II clinical trial, we will test the hypothesis that CK-1827452 can improve cardiac function and hemodynamics without significantly altering myocardial oxygen consumption and thus improve cardiac efficiency as was seen preclinically.

Study Objectives

- Evaluate the effect of CK-1827452 on myocardial efficiency, defined as the ratio of ventricular performance to myocardial oxygen consumption.
- Evaluate the effects of CK-1827452 on ventricular performance, myocardial oxygen consumption, invasively measured hemodynamics including filling pressures and cardiac output, pressure-volume relationships and systolic ejection time.

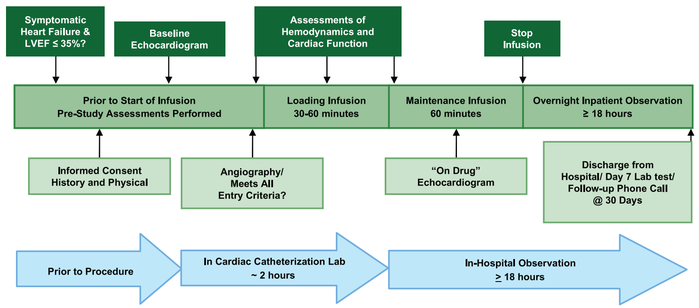
Study Population

Patients with NYHA class II or greater heart failure and left ventricular ejection fraction ≤ 35% in sinus rhythm with a clinical indication for left and right heart catheterization. Key exclusions are plans for an immediate revascularization procedure, pacemaker dependent ventricular rhythm, or acute coronary syndrome within last 30 days.

Study Design

Open-label, multi-center study performed in the cardiac catheterization laboratory in heart failure patients undergoing clinically indicated coronary angiography. Right and left heart pressures, cardiac output, coronary blood flow, aortic and coronary sinus oxygen content and pressure-volume loops using a conductance catheter will be assessed before and during administration of CK-1827452. The patients will also be evaluated non-invasively using echocardiography and acoustic cardiography. The first cohort (n=6) will undergo a dose escalation phase; the second cohort (n=12) will be evaluated under a single dose regimen selected based on the results from the first cohort and other ongoing Phase II studies of CK-1827452 in patients with heart failure.

Sequence of Events for Patients Enrolled in Study



Study Design (contd.)

Dosing Table for Cohorts 1 and 2

Cohort	N	Dose	CK-1827452 Infusion Rate (mg/hr)	Estimated Median C_{max}* (min - max) (ng/mL)	
1	6	Infusion 1: 0.5 hour loading dose Infusion 2: 1.0 hour maintenance dose	54# 21	At 0.5 hr 283 (130 - 478)	At 1.5 hrs 282 (126 - 445)
2	12	Infusion 1: ≤ 1.0 hour loading dose† Infusion 2: 1.0 hour maintenance dose	72 36	At 1 hr 594 (310 - 958)	At 2 hrs 560 (242 - 888)

* Based on data obtained from infusion of CK-1827452 in healthy subjects in Study CY 1111.

\# Starting dose.

† The loading dose infusion duration in the second cohort may be increased up to 1.0 hour if technically feasible and higher plasma concentrations are desired to achieve a larger pharmacodynamic effect. Alternatively, the infusion duration may be left equal to that of the first cohort.

Discussion

- For a novel drug mechanism, translation of preclinical findings to the clinical setting is important to support the validity of the therapeutic hypothesis on which the mechanism is based.
- A Phase I trial in healthy volunteers and a Phase II trial in patients with stable heart failure have confirmed that the novel cardiac myosin activator, CK-1827452, increases stroke volume in a manner that is tied to increasing the systolic ejection time which is the most sensitive measure of the pharmacological effect of CK-1827452[2,3].
- The current study, now initiated and enrolling, goes beyond traditional hemodynamic heart failure studies in order to comprehensively describe the effects of cardiac myosin activation on cardiac performance and myocardial energetics in patients with heart failure.
- Studies such as this one are challenging to enroll and execute but should continue to be undertaken in order to comprehensively understand the pharmacological profile of new drugs in the target patient population, in this case, patients with heart failure.

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, Page S95).

2 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. Journal of Cardiac Failure August 2007 (Vol. 13, Issue 6, Pages S145-S146).

3 Cleland JGF, et al. First Clinical Trial of the Selective Cardiac Myosin Activator, CK-1827452, in Heart Failure: Effect of Dose and Plasma Concentration on Systolic Function. European Heart Journal 2008; 29 (1):299.

CYTOKINETICS