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.

Using echocardiography in healthy volunteers’ and stable heart failure patients, we have demonstrated that in a concentration dependent manner, CK-1827452 increases Doppler derived stroke volume in a manner that is tied to directly activating cardiac myosin. In dogs with heart failure, CK-1827452 increased systolic function by increasing systolic ejection time which is the most sensitive measure of the pharmacological effect of the novel cardiac myosin activator, CK-1827452, in patients with stable heart failure.

**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 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 conductance catheter. The first cohort (n=6) will undergone 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.

**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.

**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.
- 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**

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 (3) 239.