DIRECT ACTIVATION OF CARDIAC MYOSIN BY CK-1827452 IMPROVES CARDIAC FUNCTION IN A DOG HEART FAILURE MODEL

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INTRODUCTION

Current inotropes increase intracellular calcium and secondarily increase cardiac contractility. In addition, they increase heart rate, oxygen consumption, the incidence of arrhythmias, and reduce blood pressure. A more direct approach to improving cardiac contractility that may address these liabilities is activation of cardiac myosin itself. We sought to demonstrate the therapeutic hypothesis with the orally bioavailable cardiac myosin activator, CK-1827452.

DISADVANTAGES OF CURRENT INOTROPES...

• Development of new class of drugs that are selective for cardiac myosin

ADVANTAGES OF CARDIAC MYOSIN ACTIVATORS...

• Development of new class of drugs that are selective for cardiac myosin

OBJECTIVES

• Demonstrate that the cardiac myosin activator, CK-1827452, improves cardiac function in a manner consistent with the therapeutic hypothesis

APPROACH

Discovery and Optimization of Cardiac Myosin Activators

High Throughput screening of the cardiac sarcomere

Optimization Strategy

CK-1827452 Improves Cardiac Function and Output, Hemodynamics, and Cardiac Efficiency

RESULTS

• Efficient: 5 targets – one screen

• Fast: 50,000 cmpds/day

• Robust: CV = 5-8%

CONCLUSIONS

CK-1827452 is a cardiac myosin activator that:

1) Selectively activates cardiac myosin

2) Increases contractility in cardiac myocytes without changing the calcium transient

3) Improves cardiac function and output, hemodynamics and efficiency in a dog model of heart failure and fulfills the therapeutic hypothesis

A first-in-human, Phase I, double-blind, randomized, placebo-controlled, dose-escalation, pharmacokinetic and pharmacodynamic study of CK-1827452 in healthy volunteers started earlier in September.