**Introduction**

CK-1827452 (CK-452) is a small molecule designed to improve cardiac function by the novel mechanism of directly activating cardiac myosin. In healthy subjects, CK-452 increases systolic ejection time (SET), stroke volume (SV), fractional shortening (FS), and ejection fraction (EF).

This multi-center, double-blind, placebo-controlled trial sought to assess the effects of CK-452 in patients with stable heart failure.

**Objectives**

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

**Methods**

This first Phase II trial of CK-452 was a multi-center, double-blind, randomized, placebo-controlled study in stable heart failure patients treated with an ACE inhibitor (or ARB) and a beta-blocker.

In Cohorts 1-4, patients each received four treatments: three escalating doses of CK-452 and one placebo treatment which was randomized into the dosing sequence to maintain blinding. Each of the four treatments was at least one week apart. In Cohort 5, patients received two 72-hour treatments, CK-452 and placebo in a double-blind crossover fashion. The dosing scheme is shown below.

**Results**

Dosing Table for Cohorts 1-5

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Loading Dose (mg/kg)</th>
<th>Maintaining Dose (mg/kg)</th>
<th>Entry BP of Cohort Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>60</td>
<td>Mean Arterial Blood Pressure 120/80 or systolic blood pressure ( \geq 130 \text{ mmHg} ) and diastolic blood pressure ( \geq 80 \text{ mmHg} )</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>120</td>
<td>Mean Arterial Blood Pressure 120/80 or systolic blood pressure ( \geq 130 \text{ mmHg} ) and diastolic blood pressure ( \geq 80 \text{ mmHg} )</td>
</tr>
<tr>
<td>3</td>
<td>240</td>
<td>240</td>
<td>Mean Arterial Blood Pressure 120/80 or systolic blood pressure ( \geq 130 \text{ mmHg} ) and diastolic blood pressure ( \geq 80 \text{ mmHg} )</td>
</tr>
<tr>
<td>4</td>
<td>480</td>
<td>480</td>
<td>Mean Arterial Blood Pressure 120/80 or systolic blood pressure ( \geq 130 \text{ mmHg} ) and diastolic blood pressure ( \geq 80 \text{ mmHg} )</td>
</tr>
<tr>
<td>5</td>
<td>800</td>
<td>800</td>
<td>Mean Arterial Blood Pressure 120/80 or systolic blood pressure ( \geq 130 \text{ mmHg} ) and diastolic blood pressure ( \geq 80 \text{ mmHg} )</td>
</tr>
</tbody>
</table>

**PK/PD Summary**

- At >100 ng/mL:
  - Systolic ejection time (SET) is increased
  - Fractional shortening (FS) is increased
- At >200 ng/mL:
  - Doppler-derived stroke volume (SVDo) and stroke volume (SV) are increased
  - Heart rate starts to decrease as stroke volume goes up
- At >300 ng/mL:
  - Doppler-derived cardiac output (CODo) is increased
- EF is increased
- LV end systolic and diastolic volumes (LVEF, LVED) start to decrease, possibly due to unloading of the ventricle
- At >400 ng/mL:
  - Increases in stroke volume and cardiac output plateau
- CK-452 mediated changes in cardiac function appear persistent over 24 hours

**Safety**

- Three SAEs (only one deemed related to CK-452):
  - Non-ST elevation MI in a patient with a drug overdose
  - Septicemia in setting of diabetic foot ulcer
  - Pulmonary edema

- For patients tolerant of all study drug infusions, no consistent pattern of adverse events with either dose or duration of infusion emerged

**Incidence of Treatment-Emergent Adverse Events Occurring in 2 or More Patients**

**Conclusions**

CK-452 decreases left ventricular and systolic and diastolic volumes in a concentration-dependent manner, which may be a consequence of decreases in filling pressures that could result in reverse remodeling with chronic dosing.

CK-452 is being generally well tolerated in stable HF patients over a broad range of plasma concentrations during multidose intravenous administration.

4) These findings 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.

**References**