This first Phase II trial of CK-452 is a multi-center, double-blind, randomized, placebo-controlled study in patients with EF < 40% and treated with an ACE inhibitor (or ARB) and a beta-blocker, ± diuretics. Cohorts of 8 completed patients each receive 3 infusions of escalating doses of CK-452 and 1 placebo treatment, which is randomized into the sequence to maintain blinding. Each of the four infusions are at least 1 week apart. Duration of infusion was 2 hours in Cohorts 1 and 2, and 24 hours in Cohort 3.

In an analysis of data from Cohorts 1 and 2, and data from a pre-specified interim analysis for Cohort 3 (n = 6), echocardiographic data were paired with coincident measured plasma concentrations of CK-452 to perform a pharmacokinetic/pharmacodynamic analysis.

There were statistically significant correlations between concentration and increases in SET, Stroke Volume (SV) (each p < 0.0001), Fractional Shortening (FS) and Cardiac Output (CO) (p < 0.01). Changes in EF did not achieve statistical significance. Heart rate declined slightly at the higher concentrations and there were no dose-related changes in blood pressure. Treatments were well tolerated at pre-specified dosages.

Changes in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were not statistically significant. Isovolumic relaxation time (IVRT) increased at higher concentrations. There was no change in isovolumic contraction time (IVCT). The ratio of early to late mitral filling (E/A) decreased, largely due to an increase in the atrial component of diastolic filling. Mitral valve deceleration time (MVDt) did not show consistent changes.

**REFERENCES**