Purpose: Ejection fraction (EF) remains a standard measure of left ventricular function in heart failure. Stroke volume by Doppler interrogation of the left ventricular outflow tract (LVOT SV) is more accurately measured than EF by the standard 2D image-derived Method of Discs (MoD), but it is not as familiar as EF. CK-452 increases LVOT SV in heart failure patients by prolonging systolic ejection time (SET). We compared EF changes calculated by “hybrid” methods (employing both Doppler and 2D data) to EF changes calculated by MoD for patients receiving CK-452.

Methods: Using echos obtained before, during and after infusion of the selective cardiac myosin activator, CK-452, EF was assessed by MoD and by Doppler derived LVOT SV as a percentage of ventricular volumes assessed by MoD.

Results: EF by MoD did not increase significantly; hybrid EFs increased significantly at [CK-452]-300 ng/ml. Correlation (r-square) of change from baseline in EF vs. change from baseline in SET was 0.73 (p=0.002) for EF by MoD, 0.77 (p=0.0001) for the hybrid EF based on left ventricular end-diastolic volume (LVEDV) and 0.83 (p=0.0001) for the hybrid EF based on left ventricular systolic volume (LVESV).

Conclusions: Hybrid EF calculations relating Doppler-derived LVOT SV to a 2D-imaged ventricular volume may be more sensitive to increases in systolic function than assessments of EF based entirely on 2D imaging.

**Abstract**

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

From across the five cohorts, a total of 564 echocardiograms and coincident plasma samples for measurement of CK-452 concentrations were obtained before, during and after infusion of CK-452. EF was assessed by MoD and by each of two “hybrid” methods that employed both Doppler-derived LVOT SV and ventricular volumes assessed by MoD:

**Methods**

- EFHYB-EDV = (LVOT SV/LVEDV) x 100
- EFHYB-ESV = (LVOT SV/LVESV + LVOT SV) x 100

**Results**

- **Placebo Corrected Changes from Baseline**
  - EFHYB-EDV (%) 0.8 3 < 0.0001
  - EFHYB-ESV (%) 0.8 9 < 0.0001

- **Ejection Fraction versus Systolic Ejection Time**
  - EFMOD (%) 0.80 < 0.0006
  - EFHYB-EDV (%) 0.83 < 0.0001
  - EFHYB-ESV (%) 0.89 < 0.0001

**Conclusions**

- CK-452 increases systolic ejection time, stroke volume, cardiac output, and EF in a concentration-dependent manner.
- While ejection fraction by all three methods increased with the plasma concentration of CK-452, increases of greater magnitude were observed with the hybrid methods.
- As expected, ejection fraction assessed by MoD methods that employ a measurement of stroke volume based on Doppler interrogation of the left ventricular outflow tract correlates much better with systolic ejection time (a measurement of stroke volume based on a 2D-modeling technique) than does ejection fraction assessed by the hybrid methods.
- Ejection fraction by the hybrid method based on left ventricular end-diastolic volume was slightly better correlated with systolic ejection time than the hybrid EF based on left ventricular end-systolic volume.

**References**

- Malik FI, Saikali KG, Clark CF, Teerlink JR, Wolf A. Systolic Ejection Time is a Sensitive Indicator of Left Ventricular Systolic Function During Treatment with the Selective Cardiac Myosin Activator, CK-1827452. 2007 Annual Heart Failure Society of America Meeting, Washington, DC, September 7, 2007.