Echocardiographic Detection of Increases in Ejection Fraction in Patients with Heart Failure Receiving the Selective Cardiac Myosin Activator, CK-1827452

JH. Goldman, JR. Teerlink, KG. Saikali, F. Malik, AA. Wolff

1ICON Medical Imaging, Warrington, United States of America; 2University of California, San Francisco, San Francisco, United States of America; 3Cytokinetics, Inc., South San Francisco, United States of America

ABSTRACT

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-1827452 (CK-452) increases LVOT SV in heart failure patients by prolonging systolic ejection time (SET). This first Phase II trial of CK-452 was a multi-center, double-blind, randomized, placebo-controlled trial of heart failure patients treated with an ACE inhibitor (or ARB) and a beta-blocker, ± 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 CK-452. EF was assessed by MoD and by each of two “hybrid” methods that employed both Doppler-derivived LVOT SV and ventricular assessments by EF based entirely on 2D imaging.

RESULTS

Results: EF by MoD did not increase significantly; hybrid EFs increased significantly at (CK-452) >300 ng/mL. Correlation (r²) of change from baseline in EF vs. change from baseline in SET was 0.73 (p<0.01) for EF by MoD, 0.77 (p<0.001) for the hybrid EF based on left ventricular end-diastolic volume (LVEDV) and 0.83 (p<0.001) for the hybrid EF based on left ventricular end-systolic volume (LVESV).

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

EJECTION FRACTION VERSUS SYSTOLIC EJECTION TIME

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation (r²)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF MoD (%)</td>
<td>0.80</td>
<td>0.0006</td>
</tr>
<tr>
<td>EF Hybrid (%)</td>
<td>0.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF LVESV (%)</td>
<td>0.89</td>
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* Correlations are calculated using ejection fraction by the indicated method versus systolic ejection time (SET) measured by Doppler interrogation of the left ventricular outflow tract for each patient.

CONCLUSIONS

• CK-452 increases systolic ejection time, stroke volume, cardiac output, and left ventricular ejection fraction 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 hybrid 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 derived from Doppler interrogation of the left ventricular outflow tract) than does ejection fraction assessed by the MoD method.

• Ejection fraction by the hybrid method based on left ventricular end-systolic volume was slightly better correlated with systolic ejection time than the hybrid method based on left ventricular end-diastolic volume.

REFERENCES

1 Malik FI, Saikali KG, Clark CP, Teerlink RJ, Wolff AA. 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, 2007.

ECHO PK/BD RELATIONSHIP: POOLED ANALYSIS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Baseline Corrected Changes from Baseline</th>
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<tr>
<td>EF MoD (%)</td>
<td>16 ± 4</td>
<td>18 ± 4</td>
<td>0.375</td>
<td>&lt;0.001</td>
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<tr>
<td>EF Hybrid (%)</td>
<td>18 ± 4</td>
<td>20 ± 4</td>
<td>0.465</td>
<td>&lt;0.001</td>
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<tr>
<td>EF LVESV (%)</td>
<td>19 ± 4</td>
<td>21 ± 4</td>
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ECHO CARDIOGRAPHIC DETECTION OF INCREASES IN EJECTION FRACTION IN PATIENTS WITH HEART FAILURE RECEIVING THE SELECTIVE CARDIAC MYOSIN ACTIVATOR, CK-1827452

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