### STUDY INVESTIGATORS

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### REFERENCES

1. Malki, L. I., Saitliev, L., Bublin, S. E., Chumburidze, V., Kakhidze, M., Merkuryev, A. V., 

2. Malki, L. I., Saitliev, L., Bublin, S. E., Chumburidze, V., Kakhidze, M., Merkuryev, A. V., 

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### CONCLUSIONS

1. In heart failure patients with ischemic cardiomyopathy and angina who the therapy would be most vulnerable to SE progression, treatment with CK-452 at concentrations that increase cardiac function did not deleteriously affect a broad range of safety assessments in the setting of exercise.

2. Results of this study, together with previous studies evaluating the pharmacodynamic effects of CK-452 in healthy volunteers and stable heart failure patients, support further clinical assessment of CK-452 in patients with acute and chronic heart failure.

### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Placebo</th>
<th>CK-452 Cohort 1</th>
<th>CK-452 Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>62 (8)</td>
<td>61 (8)</td>
<td>61 (8)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>33 (72)</td>
<td>32 (75)</td>
<td>33 (72)</td>
</tr>
<tr>
<td><strong>Body weight, mean (SD), kg</strong></td>
<td>83.6 (14.1)</td>
<td>83.0 (14.3)</td>
<td>83.4 (14.5)</td>
</tr>
<tr>
<td><strong>Body mass index, mean (SD), kg/m²</strong></td>
<td>29.8 (5.2)</td>
<td>29.7 (5.2)</td>
<td>30.0 (5.3)</td>
</tr>
<tr>
<td><strong>Body surface area, mean (SD), m²</strong></td>
<td>1.85 (0.18)</td>
<td>1.86 (0.18)</td>
<td>1.86 (0.18)</td>
</tr>
<tr>
<td><strong>LVEF, mean (SD), %</strong></td>
<td>48 (10)</td>
<td>48 (10)</td>
<td>48 (10)</td>
</tr>
<tr>
<td><strong>LVEDD, mean (SD), mm</strong></td>
<td>55 (9)</td>
<td>55 (9)</td>
<td>55 (9)</td>
</tr>
<tr>
<td><strong>Heart rate, mean (SD), beats per minute</strong></td>
<td>72.2 (10.7)</td>
<td>72.2 (10.7)</td>
<td>72.2 (10.7)</td>
</tr>
</tbody>
</table>

### OTHER SAFETY ASSESSMENTS

- **Vital signs, ECGs**
- **Cardiac enzymes**
- **ADs and SAEs**

### ADVERSE EVENTS

- 10 patients experienced at least one treatment-emergent AE
- 29 distinct AEs, including 2 distinct SAEs
- 23 of 29 AEs were reported as mild in severity, 4 of 29 as moderate in severity, and 2 out of 29 as serious
- 16 of 29 AEs were reported as not related to treatment, 8 out of 29 as possibly related to treatment, and 7 out of 29 as probably related to treatment

### SCREEN/ENROLL

- >

- <

- <

- 4 min on ETT 1 & 2

- **LVEF** 35%  

- 12.5 mg po TID x 6 days (1 dose day 7)  

- Target Cmax 295 ng/mL

- **(N = 94)**

- >

- **Dr. Greenberg was not a CY 1221 Investigator but served as Chair of the Safety Review Committee.**

### INTRAVENOUS DOSING PERIOD

- 20 hours of IV infusion

### ORAL DOSING PERIOD

- 7 days of oral dosing

### EXERCISE DURATION BY STAGE AT BASELINE VERSUS ETT3

### SAFETY ENDPOINTS SUMMARY

- **Primary Endpoint**

- **Phases**

- **ETT 3 vs. Baseline, mean (SD), seconds**

- **Proportion Stopping ETT3 for Angina, n (%)**

- **Depression During ETT3, n (%)**

- **Cohort 1 (N = 45)**

- **Cohort 2 (N = 45)**

### EFFECTS OF CK-452 ON ECG PARAMETERS

- Changes in ECG parameters are reported as follows:

- **QT & QTc intervals, RR interval, QRS interval**

- **Blood pressure**

- **Heart rate**

- **Respiratory rate**

- **Pulse oximetry**

- **Screening**

- **Baseline**

- **Treatment**

- **During ETT3**

### METHOD STUDY DESIGN

- **Double-blind, randomized (2:1; CK-452:placebo), placebo-controlled study of 2 sequential cohorts to evaluate effect of CK-452 on symptom-limited exercise tolerance in heart failure patients with ischemic cardiomyopathy and angina**

### BASELINE CHARACTERISTICS

- **Placebo**

- **CK-452 Cohort 1**

- **CK-452 Cohort 2**

### METHODS

- **STUDY DESIGN**

- **Double-blind, randomized (2:1; CK-452:placebo), placebo-controlled study of 2 sequential cohorts to evaluate effect of CK-452 on symptom-limited exercise tolerance in heart failure patients with ischemic cardiomyopathy and angina**

### QUALITY ASSURANCE

- **Key eligibility criteria**

- **– Documented ischemic cardiomyopathy**

- **– Current history of serum lactate dehydrogenase (LDH) levels above 240 IU/L (150 IU/L in women)**

- **– NYHA Class II-III**

- **– Adequate left ventricular function (ejection fraction ≥ 35%)**

- **– Absence of baseline ECG findings suggestive of ischemia or left ventricular hypertrophy**

- **– Lack of abnormalities suggestive of conduction defects**

- **– Ability to exercise to a stage of 4 or higher on a modified Bruce protocol**

### RESULTS

- **Primary Endpoint**

- **Secondary Endpoints**

- **Other Safety Assessments**

### CONCLUSIONS

1. In heart failure patients with ischemic cardiomyopathy and angina who the therapy would be most vulnerable to SE progression, treatment with CK-452 at concentrations that increase cardiac function did not deleteriously affect a broad range of safety assessments in the setting of exercise.

2. Results of this study, together with previous studies evaluating the pharmacodynamic effects of CK-452 in healthy volunteers and stable heart failure patients, support further clinical assessment of CK-452 in patients with acute and chronic heart failure.

### Dose-limiting Toxicity

- AEs and SAEs

- **Cardiac enzymes**

- **Prolongation, treatment with**

- **Clinical symptoms**

- **Acute Coronary Syndrome during ETT3**

- **Amgion protocol revealed critical proximal LAD stenosis, and patient successfully received stent placement.**

- **Local lab troponin levels were elevated after PTCA prompting the second SAE of post-procedural myocardial infarction.**

- **Central lab troponin 18 hours after PTCA protocol was normal.**

- **Both SAEs were reported as unrelated to treatment by investigator.**