A First-In-Human Study of the Selective Cardiac Myosin Inhibitor, CK-3773274

Laura A. Robertson,1 Danielle R. Armas,2 Edward Robbie,1 Anna Osmukhina,1 Hanbin Li,1 Fady I. Malik,1 Scott D. Solomon3

1Cytokinetics, Inc., South San Francisco, CA; 2Celero, Inc., Tempe, AZ; 3Ceritana, Inc., Menlo Park, CA; 4Brigham and Women’s Hospital, Boston, MA

INTRODUCTION

CK274 is a selective cardiac myosin inhibitor undergoing evaluation for the treatment of systolic heart failure. Preclinical studies have shown CK-274 prevents myocardial contractile dysfunction and reduces myocardial wall stress and LV mass in animal models. A study of healthy participants is required to better understand its pharmacokinetics and safety.

METHODS

Study Design

This was a Phase 1, randomized, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study to evaluate the safety and tolerability of single and multiple ascending doses of CK-274. The study included 84 healthy participants randomized to receive placebo or one of 5 doses of CK-274 (10 mg qd, 30 mg qd, 50 mg qd, 7.5 mg qd x 14d, and 40 mg). Cytokinetics, Inc., South San Francisco, CA; 2Celero, Inc., Tempe, AZ; 3Ceritana, Inc., Menlo Park, CA; 4Brigham and Women’s Hospital, Boston, MA

STUDY OBJECTIVES

Primary Objective: Identify dose(s) of CK-274 that reduce left ventricular ejection fraction (LVEF) 10% or more on the basis of multiple core laboratory assessments of echocardiograms obtained after a single dose and within 24–48 hours following 14 days of dosing.

Secondary Objectives:

• Safety
• Efficacy
• Pharmacokinetics

STUDY DESIGN

• Single Ascending Dose (SAD)
• Multiple Ascending Dose (MAD)

RESULTS

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 12)</th>
<th>MAD CK-274 (n = 6)</th>
<th>Median Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m2)</td>
<td>26.4 (4.9)</td>
<td>25.8 (4.3)</td>
<td>10 mg (6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.6 (10.5)</td>
<td>71.5 (10.4)</td>
<td>10 mg (6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36 (11)</td>
<td>37 (11)</td>
<td>25 (6)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>42</td>
<td>42</td>
<td>42</td>
</tr>
</tbody>
</table>

Safety

17 participants experienced TEAEs

• 1 participant withdrew consent
• 1 participant required dose interruption

Adverse Events

• TEAEs reported in 10 or more of 54 patients treated with CK-274

MAD Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MAD CK-274 (ng/mL)</th>
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<tbody>
<tr>
<td>Cmax</td>
<td>2,000</td>
</tr>
<tr>
<td>Cmin</td>
<td>0</td>
</tr>
<tr>
<td>AUC24</td>
<td>3,000</td>
</tr>
<tr>
<td>T1/2 max</td>
<td>81 hours</td>
</tr>
</tbody>
</table>

Phase 2 Overview

Study Schedules

• Primary objective: Safety and tolerability
• Secondary objective: Efficacy
• Dose escalation: Every patient followed by biweekly visits

Study Population

• Men and women between 18 and 70 years of age
• Participants with normal LVEF (≥50%)
• Eligibility criteria include a resting LVOT gradient ≥50 mmHg

CONCLUSIONS

CK-274 was safe and well tolerated in healthy participants; there were no SAEs and no clinically significant changes in vital signs, ECGs, or laboratory tests.

End of Study

No participants have an LVEF < 45% (unless determined not to be related to the study drug by the DLRC and investigator) and have symptoms of decreased cardiac function that appear to be related to the study drug

Acknowledgments

The authors thank all the patients who volunteered for this study and their family members.

Disclosures

• No personal information is stored.
• Visit http://bit.ly/2KEPPQ5 to obtain a PDF of this poster.

REFERENCES

• Marian AJ, Braunwald E.

• End-of-study data will be presented at the 2020 American Heart Association Scientific Sessions.

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Informed consent was obtained from all participants.