**BACKGROUND**

- **CK-2017357** selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium which increases the force response of muscle to maximal input and reduces fatigability.
- Previous clinical trials of **CK-2017357** in ALS have shown an acceptable tolerability profile with dosing as the most frequently reported adverse event, and trends towards improvements in global assessments, muscle fatigability, and quality of life function.
- This clinical trial was designed to determine if the maximum tolerable total daily dose of **CK-2017357** could be increased by:
  - Dividing the daily dose into two portions (morning and evening)
  - Beginning treatment with a low dose and titrating upward to a target of 250 mg twice daily.

**METHODS**

**Study Design**
- Randomized, double-blind, and placebo-controlled.
- 7-day stabilization period for riluzole at a reduced dose of 50 mg QD
- Patients then randomized 2:1 to **CK-2017357** or placebo for 2 weeks
- **CK-2017357** titration regimens:
  - Dosing initiated at 125 mg twice daily for 7 days (250 mg total daily dose)
  - On Day 8, up titration to 125 mg in the morning and 250 mg in the evening (375 mg total daily dose)
  - On Day 15, up titration to 250 mg twice daily (500 mg total daily dose) continued through the morning dose on Day 22
- Patients who did not tolerate a dose escalation returned to the previous tolerated dose level and remained at that dose level to complete the study.
- Placebo patients underwent a similar dummy dose titration to maintain the blind.

**RESULTS**

**Adverse Events Reported by at least 3 Patients**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade</th>
<th>Placebo</th>
<th>CK-2017357 1mg/kg (n=4)</th>
<th>CK-2017357 375 mg (n=12)</th>
<th>CK-2017357 250 mg (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>3</td>
<td>1 (5.6)</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>International normalised ratio increased</td>
<td>3</td>
<td>1 (5.6)</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
</tr>
</tbody>
</table>

**Safety**

**Safety and Tolerability**
- Of 21 patients randomized to treatment with **CK-2017357**, 16 were escalated to the highest total daily dose of 375 mg and completed three weeks of dosing.
- 2 patients terminated the study prematurely while receiving the 300 mg total daily dose due to adverse events that required hospitalization:
  - 1 with ataxia and confusion believed to be related to treatment with **CK-2017357**
  - 1 with a fall believed to be unrelated to treatment with **CK-2017357**
- 1 patient was withdrawn prematurely after completing treatment at the 375 mg total daily dose of **CK-2017357** due to hospitalization with an upper respiratory infection believed to be unrelated to treatment with **CK-2017357**
- 2 patients withdrawn from study for non-serious adverse events while receiving the 250 mg total daily dose of **CK-2017357**
  - 1 with headaches
  - 1 with anorexia, decreased appetite, fatigue, diarrhea, and dizziness
- 2 patients completed the study after a downward dose titration
- Adverse events reported by at least 3 patients overall are shown in the table above.

**Clinical Outcomes**

**Clinical Outcomes – Maximal Ventilatory Volume (MVV)**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>CK-2017357 375 mg (n=12)</th>
<th>CK-2017357 250 mg (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean (SE) Change from Baseline at Day 22</td>
<td>0.92 (&lt;0.0001)</td>
<td>0.97 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

**Clinical Outcomes – ALSFRS-R**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>CK-2017357 375 mg (n=12)</th>
<th>CK-2017357 250 mg (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean (SE) Change from Baseline at Day 22</td>
<td>0.88 (&lt;0.0001)</td>
<td>0.90 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

**ACKNOWLEDGEMENTS**

We acknowledge the contributions of Taoa Koitani, Alice Sabath-Terry, Brad Fugate, Dr. Jane Schmeltz, MD, John M. Mulder, PhD, Tudy Malick MS, PhD at Cytokinetiks, Inc. and others.