Tirasemtiv, a fast skeletal muscle troponin activator, sensitizes the sarcomere to calcium and amplifies the muscle response to submaximal nerve stimulation. It is being developed to improve skeletal muscle function in Amyotrophic Lateral Sclerosis (ALS).

Tirasemtiv is a Small Molecule Activator of the Skeletal Sarcomere

**RESULTS**

- In all completed studies, tirasemtiv appeared generally safe and well tolerated

**BENEFIT-ALS**

- Number of Subjects Included: 227
- Declined more slowly over 12 weeks on tirasemtiv versus placebo (p < 0.0001)
- The Muscle Strength Mega-Score (percent change from baseline) also declined more slowly on Tirasemtiv versus placebo (p=0.016 for the difference in slope of decline).

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**SVC by Maximum Tolerated Dose in BENEFIT-ALS**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>Tirasem/g415v Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>Placebo 250 mg</td>
</tr>
<tr>
<td>SVC Change from Baseline (percentage points)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>p-value</td>
<td>0.79</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Dose response cannot be interpreted because patients were not randomized to these tirasemtiv dose levels, but adjusted according to tolerability. %: better understand the relationship between dose and the effect of tirasemtiv on SVC, patients must be randomized to specific target dose levels.

**Major Lessons Learned from BENEFIT-ALS**

- BENEFIT-ALS is the first clinical trial of use to demonstrate a positive and potentially clinically meaningful effect on measure of respiratory and skeletal muscle function
- The effect of tirasemtiv on SVC in BENEFIT-ALS is robust and should be confirmed and extended in a larger trial
- Similar in magnitude across all subgroups evaluated (but numerically larger in patients with more rapidly declining baseline SVC)
- Statistically significant within the majority of subgroups evaluated
- The open-label lead-in period succeeded in preserving the blind after randomization but did not succeed in minimizing drop-outs after randomization
- Tirasemtiv may have cumulative and longer term pharmacologic effects

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**VITALITY-ALS: Study Schematic**

- Screening: 2 Weeks
- Open Label Phase: 4 weeks
- Double-Blind, Placebo-Controlled Phase: 48 Weeks
- Double-Blind, Placebo-Controlled, Tirasemtiv Withdrawal Phase: 4 More Weeks
- Follow-Up: 4 Weeks

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**VITALITY-ALS: Study Overview**

- Multi-national, double-blind, randomized, placebo-controlled, stratified, parallel group study of 48 weeks of double-blind dosing of tirasemtiv in ALS patients who tolerate two weeks of tirasemtiv 250 mg BID
- Primary Endpoint:
  - The change from baseline to week 24 of the double-blind, placebo-controlled phase in percent predicted Slow Vital Capacity (SVC)
- Key Secondary Endpoints:
  - Time to the first occurrence of a decline in percent predicted SVC > 20 percentage points or the onset of respiratory insufficiency or death during all 48 weeks of double-blind, placebo-controlled treatment
  - Time to the first occurrence of a decline in percent predicted SVC > 20 percentage points or the onset of respiratory insufficiency or death during all 48 weeks of double-blind, placebo-controlled treatment
  - Time to the first occurrence of a decline in the respiratory components of the ALSFRS-R in patients who had a baseline score of 9

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**VITALITY-ALS: Study Design Overview**

- Three phases of the study
  - Open-label: 125 mg tirasemtiv twice daily for 2 weeks
  - Double-Blind, Placebo-Controlled: 12.5 mg/day
    - Double-Blind, Placebo-Controlled: 250 mg/day
      - Double-Blind, Placebo-Controlled: 500 mg/day
      - Double-Blind, Placebo-Controlled: 750 mg/day
  - Follow-Up: 4 Weeks

**VITALITY-ALS: Phase III Clinical Trial of Tirasemtiv**

Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices of Treatment for a Year in ALS (VITALITY-ALS): Study Design of a Phase III Clinical Trial of Tirasemtiv in ALS


Cytokinetix, Inc., South San Francisco, CA, USA; Barnrow Neurological Institute, Phoenix, AZ, USA

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**METHODS**

- **VITALITY-ALS is planned to be conducted in >75 centers in 11 countries:**
  - **USA**
  - **Canada**
  - **France**
  - **Germany**
  - **Ireland**
  - **Italy**
  - **Netherlands**
  - **Portugal**
  - **Spain**
  - **UK**
  - **USA**

- **The start of VITALITY-ALS was announced in July 2015 and is planned to complete in 2017.**