Tirasemtiv (CK-2017357): A Selective Fast Skeletal Muscle Troponin Activator for the Potential Treatment of ALS

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Abstract

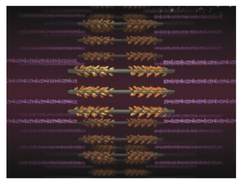
Introduction: *Tirasemtiv* (CK-2017357), a novel small molecule that is highly selective for the fast skeletal muscle troponin complex, sensitizes the sarcomere to calcium by slowing calcium release from the regulatory troponin complex. As a result, *tirasemtiv* increases fast skeletal muscle force production, especially at low to mid-range neuronal stimulation frequencies. In addition, *tirasemtiv* delays the onset and reduces the magnitude of fatigue during sustained fast skeletal muscle stimulation. *Tirasemtiv* is being developed to improve skeletal muscle function in diseases associated with skeletal muscular weakness or fatigue such as Amyotrophic Lateral Sclerosis (ALS).

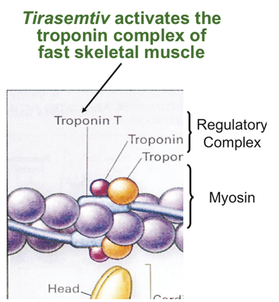
Methods: Three Phase 2a clinical trials in patients with ALS (CY4021, CY4024 and CY4025) have been completed with *tirasemtiv*. CY4021 (n=67) was a double-blind, randomized, 3-period, crossover study using single doses, administered 1 week apart and in random order, of *tirasemtiv* at 250 mg and 500 mg versus placebo. CY4024 (n=49) was a double-blind, randomized, four parallel group study of *tirasemtiv* at 125, 250 or 375 mg once daily for 14 days versus placebo. In CY4025 (n=28), patients taking *riluzole* 50 mg daily were titrated on *tirasemtiv* (versus placebo) from 125 mg twice daily to 250mg twice daily over 3 weeks in a double-blind, randomized fashion in two parallel groups.

Results: In all studies, *tirasemtiv* was generally safe and well tolerated. In CY4021, both patients and investigators perceived a statistically significant dose- and concentration-dependent improvement in patients' overall status at 6 hours after dosing. A statistically significant improvement in Maximum Voluntary Ventilation (MVV) at 6 and 24 hours after a single 500 mg dose also was observed. Sniff Inspiratory Pressure (SNIP) and sub-maximal grip endurance also trended to increase. In CY4024, plasma concentrations of *tirasemtiv* were unaffected by co-administration with *riluzole*, while plasma concentrations of *riluzole* approximately doubled with *tirasemtiv*. In all three studies, the most frequently reported and most clearly dose-related adverse event was dizziness, which was mostly mild, began early after initiation and usually resolved with continued treatment. In CY4024 and CY4025, trends to increase the ALS Functional Rating Scale-Revised score (ALSFRS-R) and MVV were observed.

Conclusions: Based on the results of the three Phase 2a trials described above, a Phase 2b clinical trial of *tirasemtiv* in ALS, BENEFIT-ALS, is currently enrolling patients. BENEFIT-ALS is a multi-national, randomized, stratified, double-blind, placebo controlled, parallel group study of 12 weeks dosing to assess the effect of *tirasemtiv* (administered twice daily at each patient's maximum tolerated dose, up to a maximum dose of 500 mg daily) on the ALSFRS-R total score.

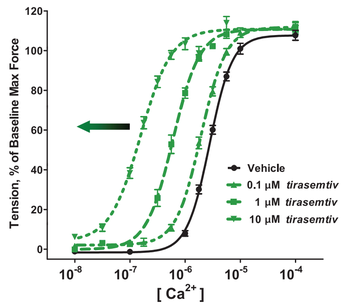
The Sarcomere: The Contractile Unit of Muscle





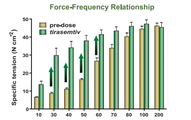
Tirasemtiv Sensitizes the Sarcomere to Calcium

Increases tension in Skinned Fast Skeletal Muscle Fibers

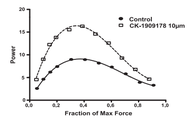


The Effects of Fast Skeletal Troponin Activation on Skeletal Muscle Function

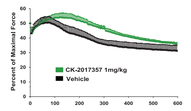
Skeletal Troponin Activators Amplify the Response to Motor Neuron Input



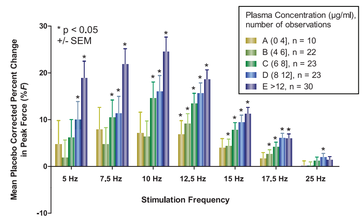
Skeletal Troponin Activators Increase Muscle Power

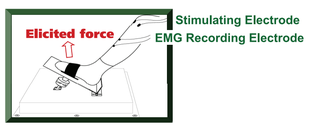


Skeletal Troponin Activators Slow the Onset and Reduce the Degree of Muscle Fatigue



Tirasemtiv Increases Contraction Force in Healthy Volunteers





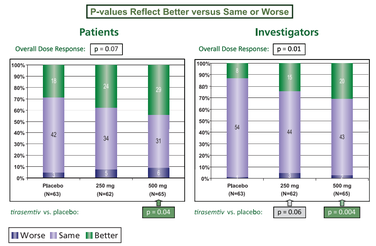
Prior Clinical Trials of *Tirasemtiv* in ALS

CY 4021 (N = 67)
- Double-blind, randomized, three period crossover
- Single doses in random order, about 1 week apart
- Placebo, *tirasemtiv* 250 mg, *tirasemtiv* 500 mg

CY 4024 (N = 49)
- Double-blind, randomized, four parallel groups
- Placebo or *tirasemtiv* at 125, 250, or 375 mg QD for 14 days
- Off *riluzole* (n = 24); *riluzole* 50 mg daily (n = 25)

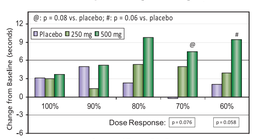
CY 4025 (N = 28)
- Double-blind, randomized, two parallel groups
- *Tirasemtiv* dose titration: 125 mg BID to 250 mg BID over 3 weeks
- Dummy dose titration with placebo
- All patients took *riluzole* 50 mg daily

CY 4021: Global Assessments at 6 Hours



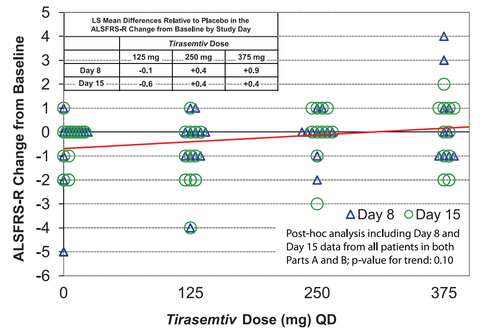
CY 4021: Other Key Findings

- **Trends to prolong sub-maximal handgrip endurance (seconds maintained above indicated percentage of target)**

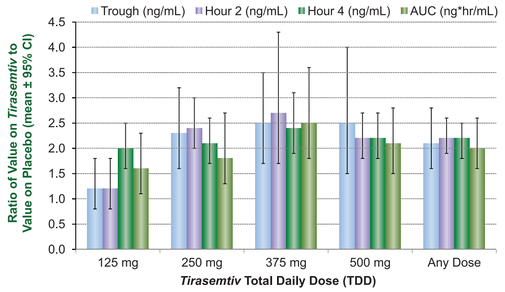


- **Maximum voluntary ventilation (MVV) increased ~ 4 L/min versus placebo at 6 and 24 hours after 500 mg ($p \leq 0.05$)**
- **Dizziness was the most frequently reported adverse event**
  - **Placebo 2/63 (3%)**
  - ***Tirasemtiv* 250 mg 13/62 (21%)**
  - ***Tirasemtiv* 500 mg 32/66 (49%)**

CY 4024: ALSFRS-R Trend to Increase with Dose



Tirasemtiv Daily Doses of 250 to 500 mg Generally Double Average *Riluzole* Exposures*



**Riluzole concentrations from CY 4024 and CY 4025*

BENEFIT-ALS

BENEFIT-ALS: Key Design Elements

Randomize 400 patients with ALS
- Randomization 1:1 *tirasemtiv* versus placebo stratified by *riluzole* use
- 12 weeks of double-blind treatment

***Tirasemtiv* titrated versus placebo BID** (similar to CY 4025)
- More flexible: dosing interruptions or down-titrations permitted
- More persistent: each titration step must be attempted at least twice

Patients taking riluzole will receive
- *Riluzole* 50 mg twice daily if randomized to placebo
- *Riluzole* 50 mg once daily if randomized to *tirasemtiv*
- The evening *riluzole* dose will be blinded to preserve the study blind

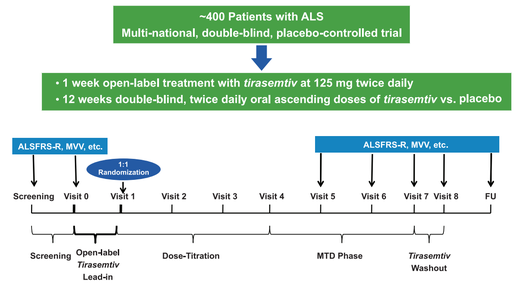
Primary endpoint
- Mean ALSFRS-R at 8 and 12 weeks
- 80% power for a 1.18 point difference vs. placebo, 2-tailed = 0.05

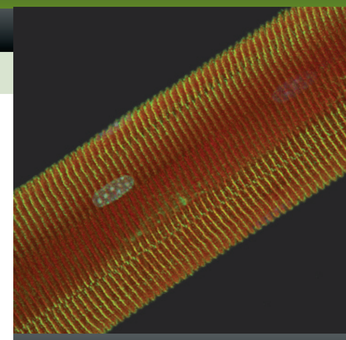
First secondary endpoint
- Maximum Voluntary Ventilation

Blinded Evaluation of Neuromuscular Effects and Functional Improvement with *Tirasemtiv* in ALS

Lead Investigator:
Jeremy M. Shefner, MD, PhD
Professor and Chair of Neurology
SUNY Upstate Medical University

Study Design





BENEFIT-ALS: Study Organization and Timeline

Leadership
- Lead Investigator: Jeremy M. Shefner, MD, PhD, SUNY Upstate
- Cytokinetics Medical Director: Jinsy Andrews, MD

Planning for more than 70 Study Centers in 7 countries
- United States
- Canada
- United Kingdom
- France
- Germany
- Netherlands
- Ireland

First patient enrolled
- 6 Nov 2012

Aiming for data presentation end of 2013

CYTOKINETICS