

TIRASEMTIV (CK-2017357): A FAST SKELETAL MUSCLE TROPONIN ACTIVATOR FOR THE POTENTIAL TREATMENT OF ALS

Jinsy A. Andrews, MD, MSc for the BENEFIT-ALS Study Group

Cytokinetics Inc, South San Francisco, CA

ABSTRACT

Introduction: *Tirasemtiv* (CK-2017357), a fast skeletal muscle troponin activator that sensitizes the sarcomere to calcium and increases the force of contraction, is the first therapy directed at improving the muscle weakness in patients with ALS.

Methods: Three Phase IIa clinical trials of *tirasemtiv* in ALS patients have been completed. CY 4021 (n=67) was a double-blind, randomized, 3-period, crossover study using single doses, 1 week apart, in random order of *tirasemtiv* at 250 and 500mg versus placebo. CY 4024 (n=49) was a double-blind, randomized, four parallel group study using *tirasemtiv* at 125, 250 or 375 mg once daily for 14 days versus placebo. In CY 4025 (n=28), patients taking *riluzole* 50mg daily were titrated from 125mg twice daily to 250mg twice daily over 3 weeks in a double-blind, randomized fashion in two parallel groups.

A Phase IIb clinical trial of *tirasemtiv* in patients with ALS, BENEFIT-ALS, is an international, randomized, double-blind, placebo controlled, parallel group study of 12 weeks dosing with *tirasemtiv* to assess its effect of on the ALS Functional Rating Scale-Revised (ALSFRS-R) total score when administered twice daily at each patient's maximum tolerated dose, up to 500mg daily.

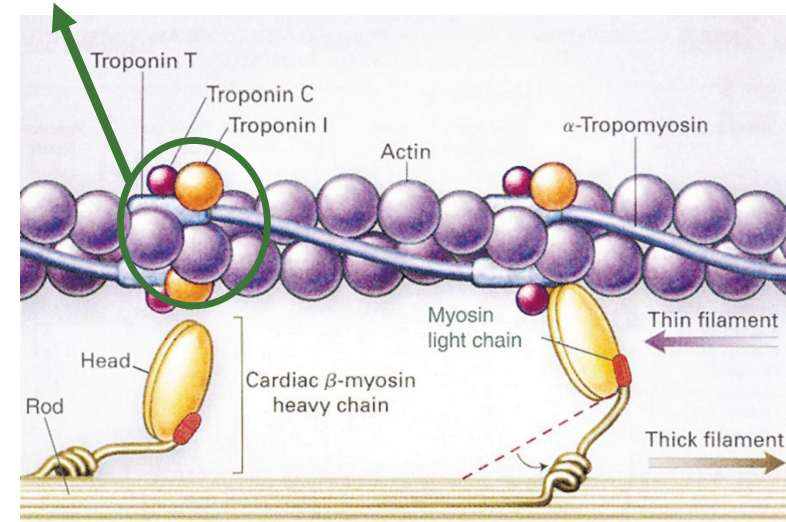
Results: In all completed studies, *tirasemtiv* appeared generally safe and well tolerated. In CY 4021, both patients and investigators perceived a dose- and concentration-dependent improvement versus placebo in patients' overall status 6 hours after dosing. In CY 4024 and CY 4025, encouraging trends to increase the ALSFRS-R and Maximum Voluntary Ventilation (MVV) versus placebo were observed.

BENEFIT-ALS implemented ALSFRS-R and quantitative measures of respiratory and extremity muscle strength and endurance in which dose- and concentration-dependent trends were observed in prior studies. During a one week open-label lead-in, all patients received *tirasemtiv* 125mg BID to ensure that randomized patients could tolerate this dose and to help maintain the blind. Patients who tolerated open-label *tirasemtiv* were randomized 1:1 to placebo or *tirasemtiv* (stratified by *riluzole* use) beginning at 125mg BID and escalating to a maximum of 250mg BID for 12 weeks of treatment.

Conclusions: BENEFIT-ALS has completed enrollment and last study visits will occur in March 2014. BENEFIT-ALS tests the hypothesis that improving skeletal muscle performance can meaningfully affect measures of function in patients with ALS.

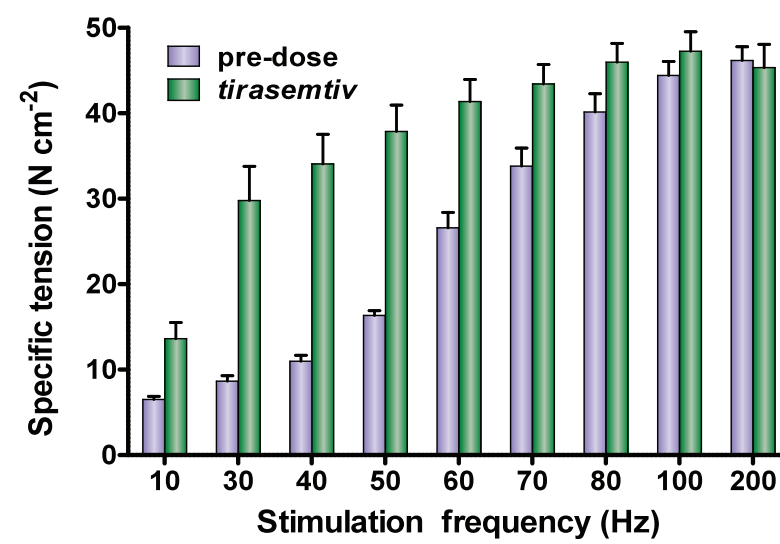
TIRASEMTIV IS A SMALL MOLECULE ACTIVATOR OF THE SKELETAL SARCOMERE

Tirasemtiv activates the troponin complex of fast skeletal muscle



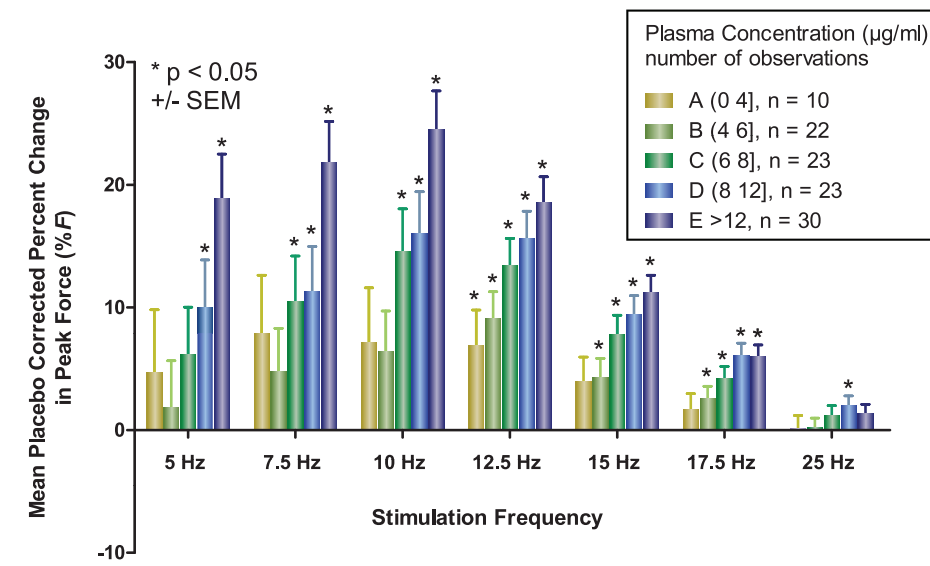
TIRASEMTIV INCREASES THE EFFICIENCY OF SUBMAXIMAL MUSCLE CONTRACTION

Force-Frequency Relationship



Data from rat extensor digitorum longus (EDL) *in situ*. Russel, et al., Nature Medicine 2012

TIRASEMTIV INCREASES CONTRACTION FORCE IN HEALTHY VOLUNTEERS



Healthy male volunteers were administered single oral doses of *tirasemtiv* at 250 mg, 500 mg and 1000 mg and matching placebo, in a randomized, 4-period crossover design, at study visits approximately one week apart. Force production by the tibialis anterior muscle during stimulation of the deep peroneal nerve was measured before and at 1, 3, 5 and 7 hours after each dose.

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

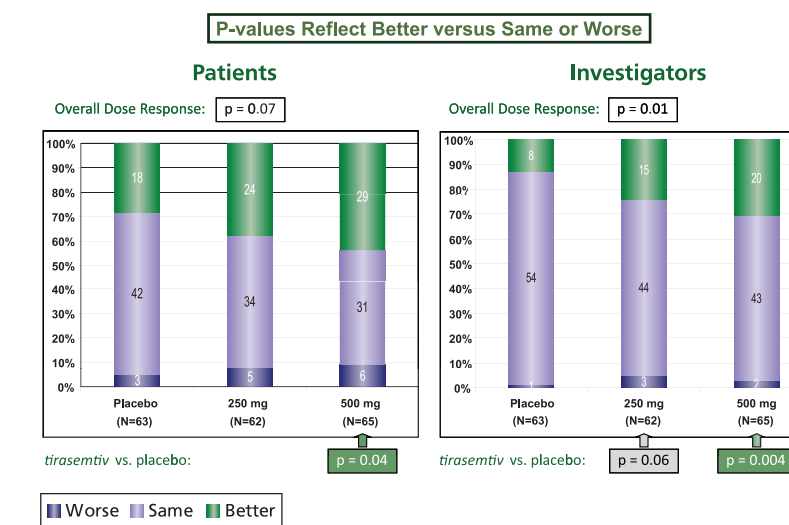
CY 4024 (N = 49)

- 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)

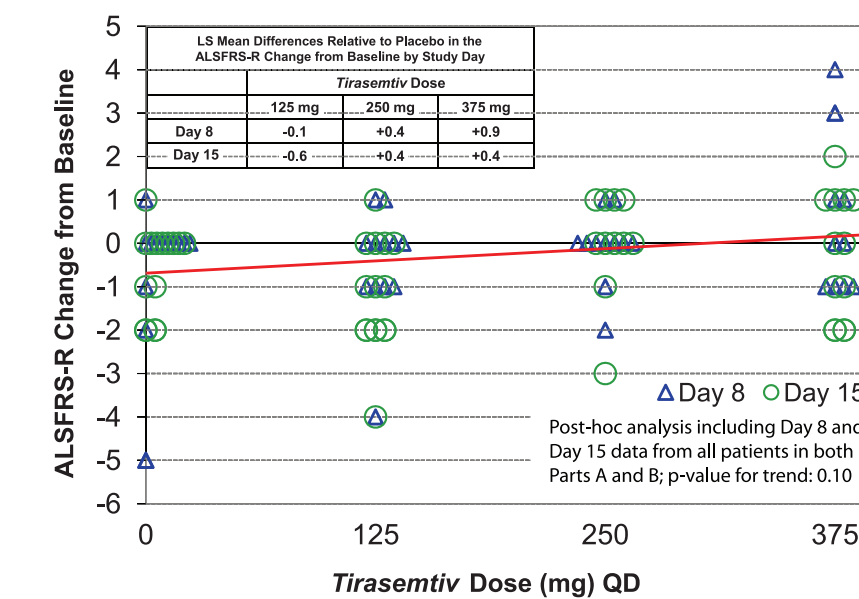
CY 4025 (N = 28)

- 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 4024: ALSFRS-R Trend to Increase with Dose



Conclusions From Completed Trials in ALS

Encouraging dose/concentration-dependent trends observed in:

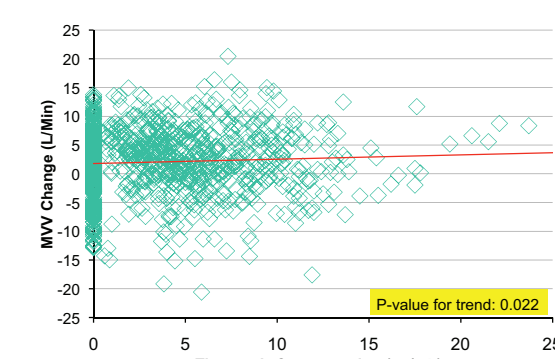
- ALSFRS-R
- Respiratory Measures
 - MVV
 - SNIP
- Quantitative Muscle Testing
- Handgrip Fatigue

Appeared generally safe and well-tolerated

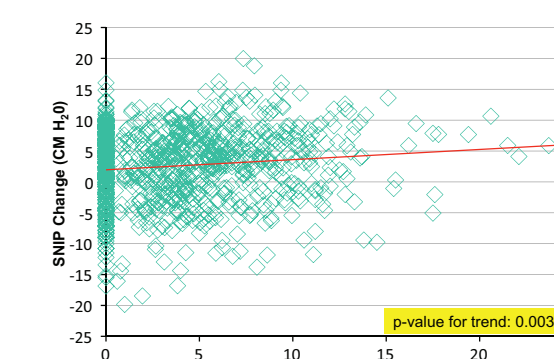
- Mild dizziness was the most common AE seen in about 40% of patients which usually abated with continued treatment

Other Key findings from Phase IIa studies in patients with ALS

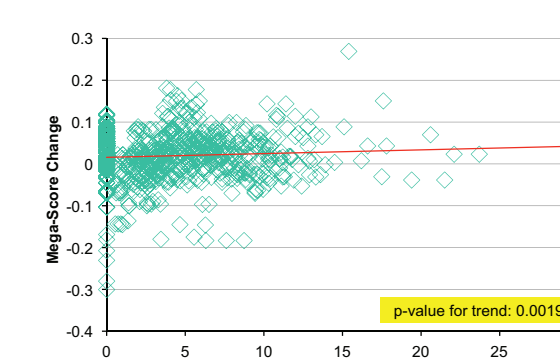
Change from Baseline in MVV versus *Tirasemtiv* Concentration



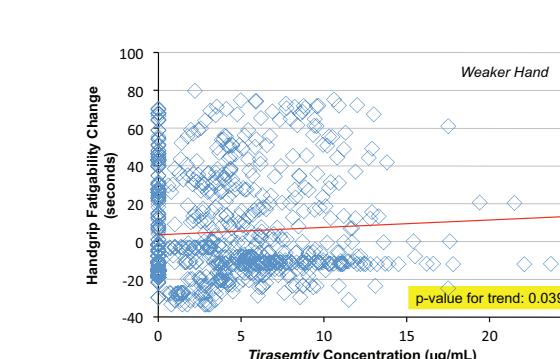
Change from Baseline in SNIP versus *Tirasemtiv* Concentration



Change from Baseline in Mega-Score versus *Tirasemtiv* Concentration



Change from Baseline in Sub-Maximal Grip Time to <60% of Target versus *Tirasemtiv* Concentration



BENEFIT-ALS

Design Considerations in BENEFIT-ALS

Goals of the Study

- Determine safety and efficacy of *tirasemtiv* administered for 3 months, at the highest tolerated dose up to 500 mg daily

Dosing

- Dose escalated weekly from 125 mg BID to 250 mg BID over 3 weeks

Addition of an open label phase

- All subjects complete 1 week of open label dosing at 125 mg BID to enrich study population and improve blinding

BENEFIT-ALS: Outcome Measures

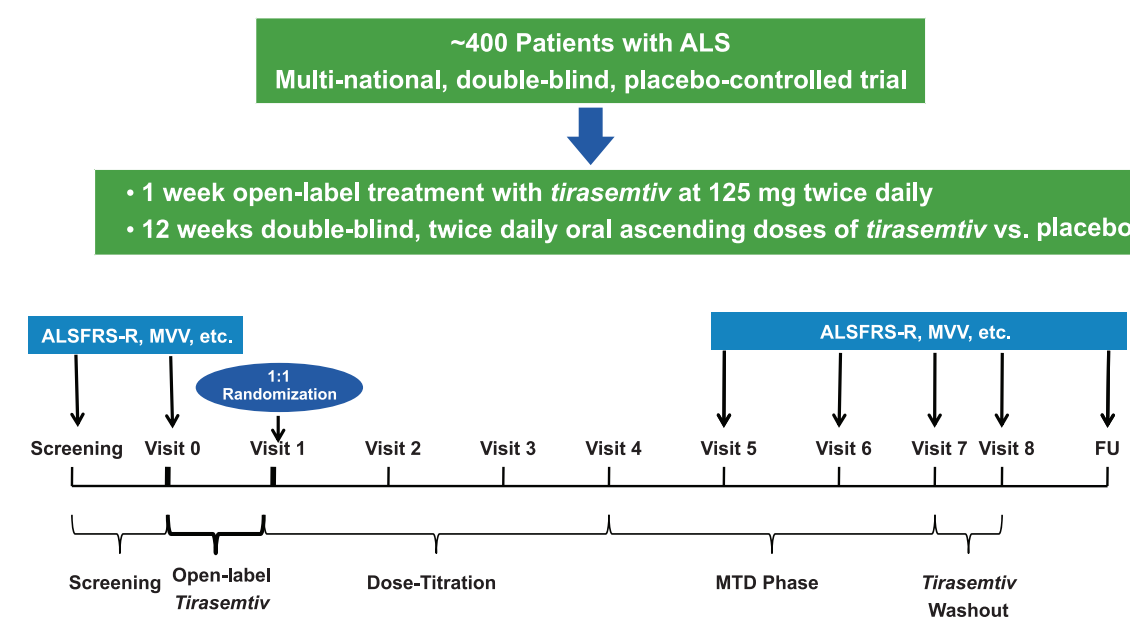
Primary:

- ALS Functional Rating Scale-Revised (ALSFRS-R)
 - Mean change in ALSFRS-R at 8 and 12 weeks
 - 80% power for a 1.18 point difference vs. placebo; 2-tailed $\alpha = 0.05$

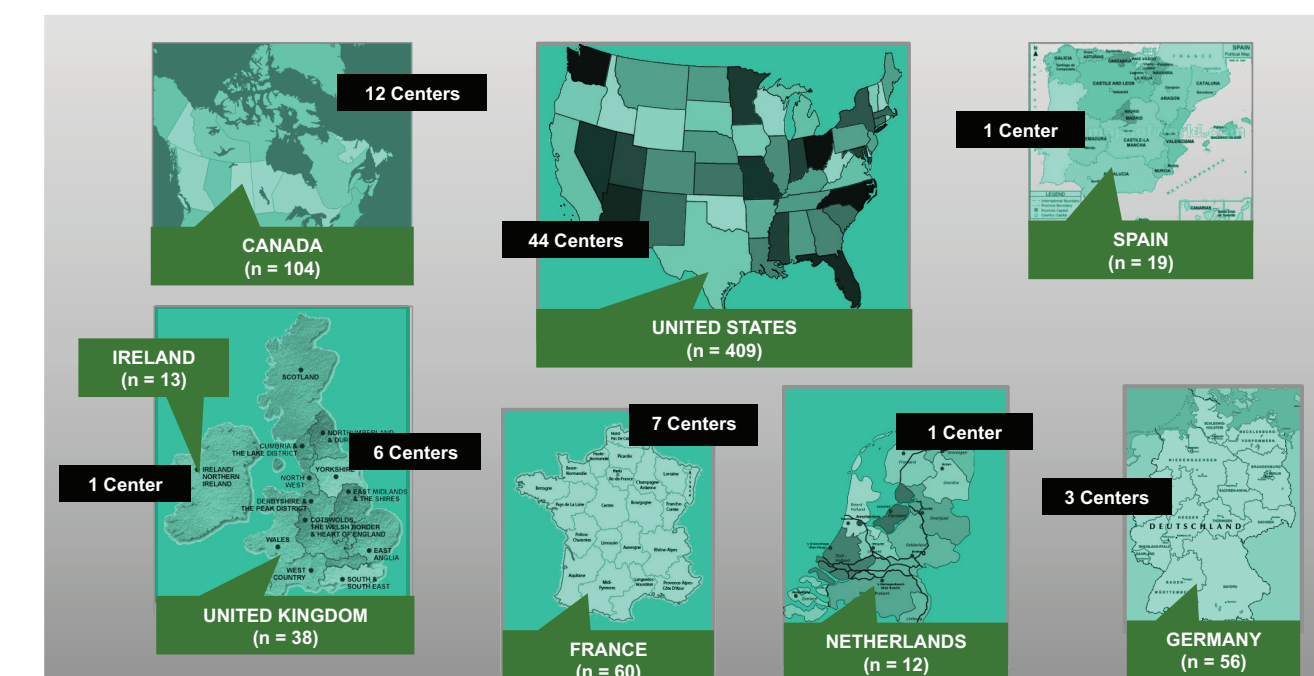
Secondary:

- ALSFRS-R endpoints for secondary analyses
- Respiratory function
 - Maximum Voluntary Ventilation (MVV)
 - Sniff Nasal Inspiratory Pressure (SNIP)
 - Slow Vital Capacity (SVC)
- Other measures of skeletal muscle function
 - Handgrip strength and fatigability
 - Muscle strength by hand-held dynamometry

Study Design



BENEFIT-ALS: Enrollment by Country



711 Patients Enrolled

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

BENEFIT-ALS: SUMMARY AND CONCLUSIONS

Leadership

- Lead Investigator: Jeremy Shefner, MD, PhD, SUNY Upstate

BENEFIT-ALS was designed with an open-label lead-in period which helps maintain blinding and outcome measures that demonstrated encouraging dose- and concentration-dependent trends in prior studies

BENEFIT-ALS is completely enrolled (711 patients)

- First patient enrolled November 2012
- Last patient enrolled November 2013
- Last patient visits to occur March 2014

Results are anticipated in the 2nd quarter of 2014