# Relationships Between *Riluzole* and *Tirasemtiv* Levels on Outcomes in the BENEFIT-ALS Trial

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## Introduction

- Earlier, small Phase 2a studies of *tirasemtiv*, a fast skeletal muscle troponin activator, suggested trends to improved function in patients with ALS
- BENEFIT-ALS was a Phase 2b study that evaluated the effects of *tirasemtiv* in 711 patients with ALS
- After 12 weeks of double-blind treatment, statistically significant differences favoring *tirasemtiv* were found in extremity strength and in slow vital capacity (SVC), although there was no significant difference between groups in ALSFRS-R

## Objective

- To examine the relationship between plasma *tirasemtiv* levels and *riluzole* levels on patient efficacy outcomes and adverse events

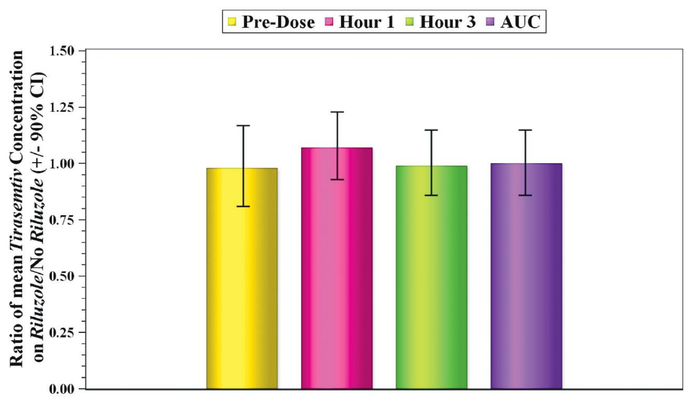
## Methods

- Enrolled patients with ALS (N = 711) began treatment with open-label *tirasemtiv* at 125 mg twice daily; 605 patients received 1 week of open label *tirasemtiv* and were randomized to placebo or an escalating dose of *tirasemtiv* to a maximum of 500 mg daily; 596 of these patients received at least one dose of double-blind study drug. Patients on *tirasemtiv* received half the labeled *riluzole* dose; i.e., 50 mg once daily. At each visit, plasma *riluzole* and *tirasemtiv* levels were obtained. Adverse events that began during open-label treatment and persisted without interruption or worsening into the double-blind treatment period were assigned to the double-blind treatment if they continued for > 96 hours after the first dose of double-blind study drug. The relationship of adverse events to *riluzole* and *tirasemtiv* concentrations was determined. Changes from baseline in ALSFRS-R, SVC, and muscle strength via hand held dynamometry (Mega-Score) were related to concentrations of *riluzole* and *tirasemtiv*; analyses based on slope of change from baseline were performed.

## Results

### *Tirasemtiv* Levels

*Riluzole* did not affect *tirasemtiv* concentrations




### Safety

*Riluzole* did not impact tolerability profile

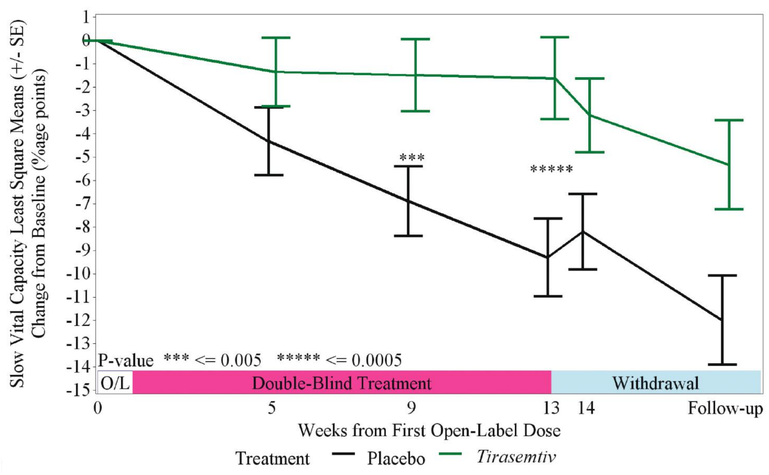
**Treatment-Emergent Adverse Events: Comparison of Adverse Events On and Off Riluzole by Descending Overall Frequency**

| Preferred term | Placebo No *Riluzole* Use (N=101) n(%) | *Tirasemtiv* No *Riluzole* Use (N=105) n(%) | Placebo *Riluzole* Use (N=194) n(%) | *Tirasemtiv* *Riluzole* Use (N=196) n(%) | Overall (N=596) n(%) |
|---|---|---|---|---|---|
| Dizziness | 18 (17.8%) | 56 (53.3%) | 40 (20.6%) | 97 (49.5%) | 211 (35.4%) |
| Fatigue | 14 (13.9%) | 43 (41.0%) | 28 (14.4%) | 57 (29.1%) | 142 (23.8%) |
| Nausea | 11 (10.9%) | 24 (22.9%) | 12 (6.2%) | 42 (21.4%) | 89 (14.9%) |
| Headache | 12 (11.9%) | 19 (18.1%) | 21 (10.8%) | 35 (17.9%) | 87 (14.6%) |
| Asthenia | 10 (9.9%) | 22 (21.0%) | 27 (13.9%) | 26 (13.3%) | 85 (14.3%) |
| Muscle spasms | 6 (5.9%) | 18 (17.1%) | 10 (5.2%) | 27 (13.8%) | 61 (10.2%) |
| Muscular weakness | 6 (5.9%) | 15 (14.3%) | 14 (7.2%) | 19 (9.7%) | 54 (9.1%) |
| Somnolence | 3 (3.0%) | 14 (13.3%) | 8 (4.1%) | 25 (12.8%) | 50 (8.4%) |
| Contusion | 8 (7.9%) | 7 (6.7%) | 17 (8.8%) | 15 (7.7%) | 47 (7.9%) |
| Insomnia | 5 (5.0%) | 16 (15.2%) | 7 (3.6%) | 15 (7.7%) | 43 (7.2%) |
| Decreased appetite | 3 (3.0%) | 11 (10.5%) | 6 (3.1%) | 19 (9.7%) | 39 (6.5%) |

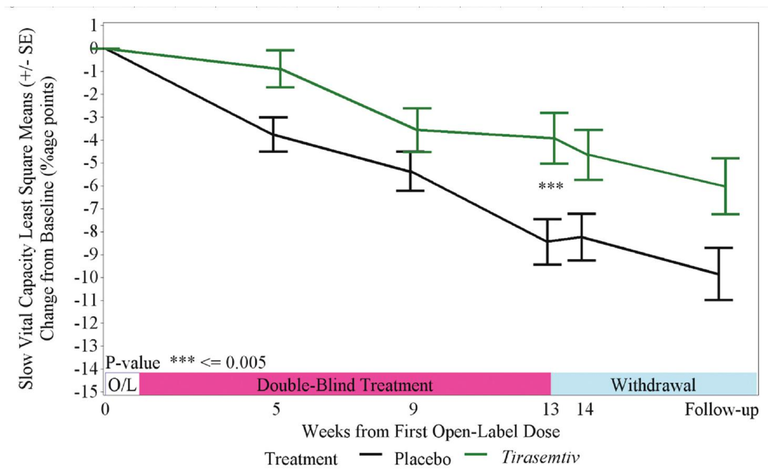
Version 15.1 of MedDRA was used to code adverse events.
n = Number of Patients with treatment-emergent adverse events.

### *Riluzole* and the Effect of *Tirasemtiv* on Slow Vital Capacity

Decline of % Predicted SVC Off *Riluzole*




Decline of % Predicted SVC On *Riluzole*

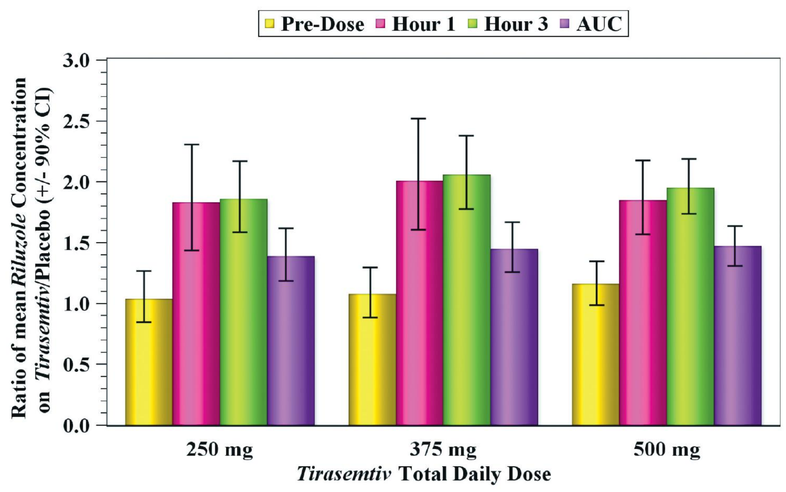



### *Tirasemtiv* Maximum Tolerated Dose and SVC at Week 12

| SVC Change from Baseline (%age points) | | *Tirasemtiv* Total Daily Dose | | |
|---|---|---|---|---|
| | Placebo | 250 mg | 375 mg | 500 mg |
| Mean (SD) Average *Tirasemtiv* Concentration | 0 | 7.97 (2.68) | 10.85 (4.54) | 12.86 (4.06) |
| LSM (SE) | -8.66 (0.80) | -1.48 (1.94) | -3.06 (1.78) | -3.58 (1.36) |
| LSM (SE) Difference from Placebo | | 7.14 (2.10) | 5.52 (1.96) | 5.07 (1.58) |
| p-value | | 0.0008 | 0.0054 | 0.0015 |

### *Riluzole* Concentrations

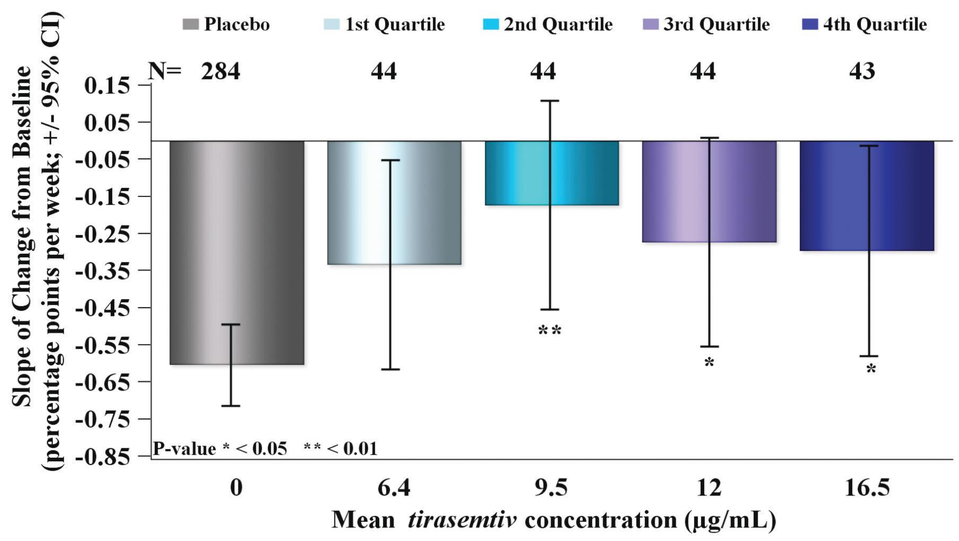
*Tirasemtiv* increased post-dose *riluzole* concentrations but not in a dose-dependent fashion




Note *riluzole* concentrations were not affected pre-dose.

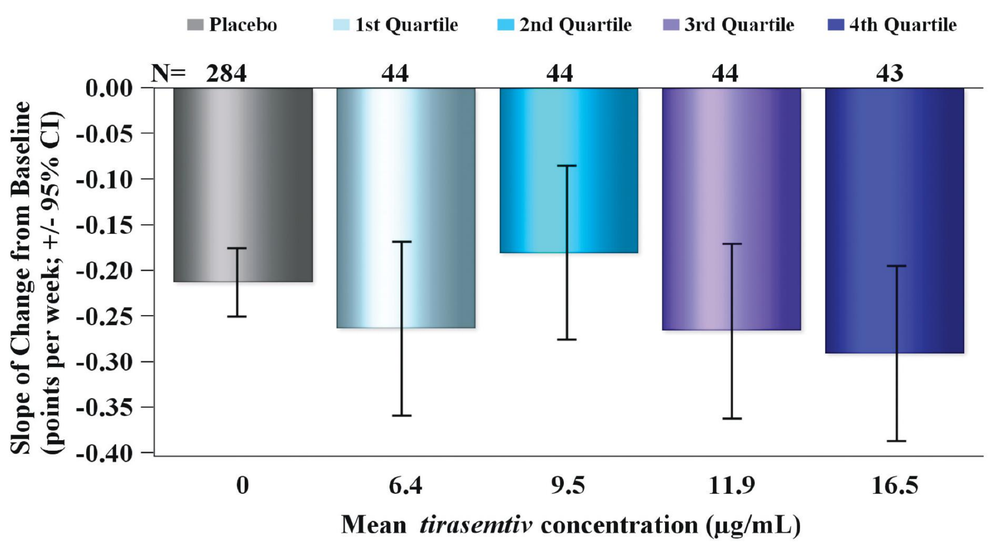
### *Tirasemtiv* Levels and SVC

Effect of *tirasemtiv* on SVC was not concentration-dependent



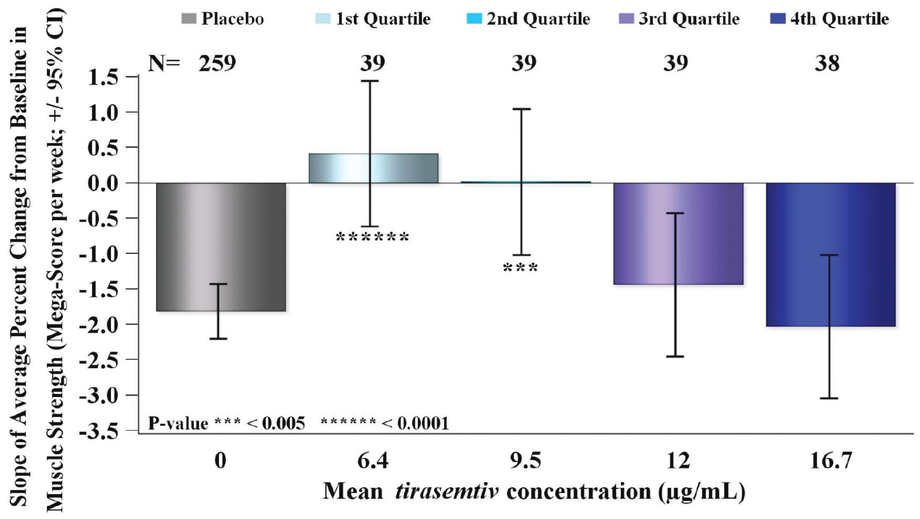

### *Tirasemtiv* Levels and ALSFRS-R

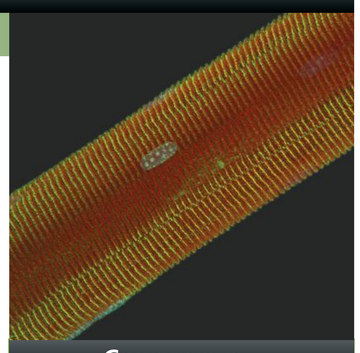
Effect of *tirasemtiv* on ALSFRS-R was not concentration-dependent




### *Tirasemtiv* Levels and Muscle Strength Measured by Hand-Held Dynamometry (HHD)

Effect of *tirasemtiv* on muscle strength may be inversely related to concentration



## Conclusions

- *Tirasemtiv* increased post-dose *riluzole* concentrations similarly at all doses of *tirasemtiv*; in patients on *tirasemtiv*, half the labeled *riluzole* dose appears to result in approximately a 50% increase in overall *riluzole* exposure as measured by area under the curve (AUC)
- *Riluzole* did not increase *tirasemtiv* plasma concentrations nor did *riluzole* impact the tolerability of *tirasemtiv*; the effect of *tirasemtiv* to reduce the decline in SVC was observed in patients both on and off *riluzole*
- *Tirasemtiv* reduced the slope of decline in slow vital capacity by approximately 50%; effects on slow vital capacity were observed at all doses studied and the concentration-response relationship was flat
- *Tirasemtiv* reduced the decline in muscle strength measured by hand-held dynamometry; however, the effect was only evident in the lower two quartiles of *tirasemtiv* plasma concentrations
- There was no effect of *tirasemtiv* on ALSFRS-R in any plasma concentration quartile
- Overall, the relationships between the plasma concentration and dose of *tirasemtiv* and its effects on slow vital capacity and muscle strength suggest that lower target doses of *tirasemtiv* than studied in BENEFIT-ALS may warrant further evaluation

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