

**RESULTS**

**Tirasemtiv Levels**

![Graph showing Riluzole did not affect tirasemtiv concentrations](image1)

Riluzole did not affect tirasemtiv concentrations.

**Tirasemtiv Concentrations**

![Graph showing Tirasemtiv increased post-dose riluzole concentrations but not in a dose-dependent fashion](image2)

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

**Decline of % Predicted SVC Off Riluzole**

![Graph showing Decline of % Predicted SVC Off Riluzole](image3)

Decline of % Predicted SVC Off Riluzole.

**Decline of % Predicted SVC On Riluzole**

![Graph showing Decline of % Predicted SVC On Riluzole](image4)

Decline of % Predicted SVC On Riluzole.

**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 on 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 upper quartile 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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**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 who began during open-label treatment and continued 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 tirasemtiv 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.

**CONFIDENTIALITY**

- The study was conducted under the guidelines of the Declaration of Helsinki.
- All patients provided written informed consent.
- The study was approved by an independent ethics committee.

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**TIRASEMTIV LEVELS AND THE EFFECT OF TIRASEMTIV ON SLOW VITAL CAPACITY**

**TIRASEMTIV LEVELS AND SVC**

![Graph showing TIRASEMTIV LEVELS AND SVC](image5)

Effect of tirasemtiv on SVC was not concentration-dependent.

**TIRASEMTIV LEVELS AND ALSFRS-R**

![Graph showing TIRASEMTIV LEVELS AND ALSFRS-R](image6)

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

**TIRASEMTIV LEVELS AND MUSCLE STRENGTH MEASURED BY HAND-HELD DYNAMOMETRY (HHD)**

![Graph showing TIRASEMTIV LEVELS AND MUSCLE STRENGTH](image7)

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

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**RILUZOLE AND THE EFFECT OF TIRASEMTIV ON SLOW VITAL CAPACITY**

**SVC Change from Baseline (%age points)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>250 mg</th>
<th>375 mg</th>
<th>500 mg</th>
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</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>LGM (SD)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.008</td>
<td>0.005</td>
<td>0.015</td>
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</table>

**TIRASEMTIV TOTAL DAILY DOSE**

<table>
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<tr>
<th>Group</th>
<th>Placebo</th>
<th>250 mg</th>
<th>375 mg</th>
<th>500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>7.97 (2.68)</td>
<td>10.85 (4.58)</td>
<td>12.85 (4.06)</td>
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</tr>
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<td>LGM (SD)</td>
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<tr>
<td>p-value</td>
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<td>0.00001</td>
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<td></td>
</tr>
</tbody>
</table>

**TIRASEMTIV MAXIMUM TOLERATED DOSE AND SVC AT WEEK 12**

![Graph showing TIRASEMTIV MAXIMUM TOLERATED DOSE AND SVC AT WEEK 12](image8)

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