Novel Data from BENEFIT-ALS (Blinded Evaluation of Neuromuscular Effects and Functional Improvement with *Tirasemtiv* in Amyotrophic Lateral Sclerosis): Effects of *Tirasemtiv* across Subgroups

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Introduction

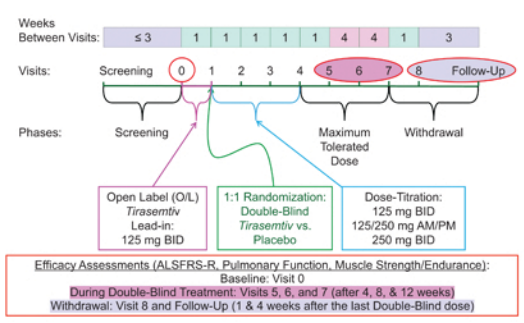
Tirasemtiv is a novel fast skeletal muscle activator that sensitizes the sarcomere to calcium and leads to an increase in the force of muscle contraction at sub-maximal neuronal stimulation frequencies. In previous studies, it was well tolerated in patients with amyotrophic lateral sclerosis (ALS), and dose dependent improvements on measures of muscle strength and patient function were noted.

Methods

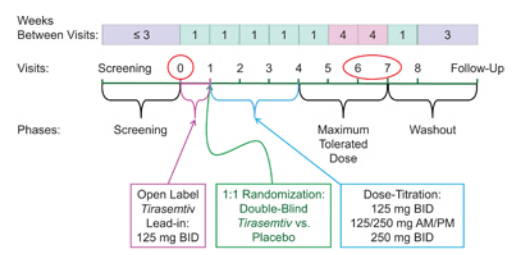
711 patients with ALS, with or without exposure to *riluzole*, were recruited from 73 centers in North America and Europe. Slow vital capacity was > 50% of predicted, at least one handgrip was moderately weak, and ≥ 4 ALSFRS-R items scored 2 or 3. Before randomization, patients received 1 week of open-label *tirasemtiv* 125 mg BID to ensure this dose was well tolerated. Patients who tolerated open-label *tirasemtiv* were then randomized 1:1 to double-blind placebo or *tirasemtiv* beginning at 125 mg BID and escalating weekly based on tolerability to a maximum of 250 mg BID for a total of 12 weeks of treatment. ALSFRS-R and quantitative measures of respiratory and extremity muscle strength and endurance were assessed at baseline, after 4, 8, and 12 weeks of treatment, and at 1 and 4 weeks after the last dose. As was specified in the statistical analysis plan as finalized before unblinding, subgroup analyses were based on the change from baseline to the average of the outcome measurements obtained at Visits 6 and 7, after 8 and 12 weeks of treatment, respectively, analogous to the primary efficacy analysis of the ALSFRS-R.

BENEFIT–ALS

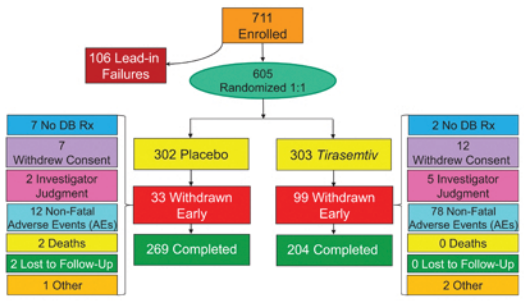
Study Design



Primary Efficacy Endpoint: ALSFRS-R



Patient Disposition



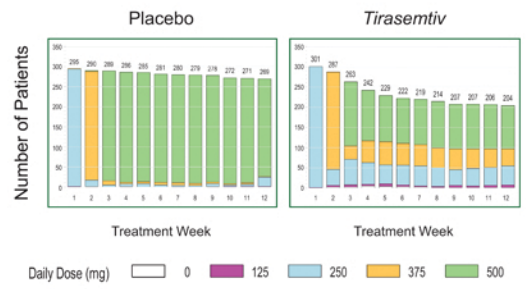
Baseline Data

Mean (SD) or n [%]	Placebo (n = 210)	*Tirasemtiv* (n = 178)	All (N = 388)
Age (years)	56.8 (10.6)	56.1 (11.7)	56.5 (11.2)
Male [%]	148 [70.5%]	131 [73.6%]	279 [71.9%]
BMI (kg/m²)	26.8 (4.4)	26.7 (4.4)	26.8 (4.4)
Months from Diagnosis	12.2 (17.1)	13.8 (20.8)	12.9 (18.9)
Months from 1st Symptom	26.7 (23.7)	30.6 (32.1)	28.5 (27.9)
ALSFRS-R Total Score	37.3 (4.2)	37.0 (4.7)	37.2 (4.4)
Slow Vital Capacity (SVC, % Predicted)*	89.7 (17.2)	85.7 (19.3)	87.8 (18.3)
Maximum Voluntary Ventilation (MVV, L/min)	75.1 (35.7)	72.6 (35.0)	74.0 (35.4)
Sniff Nasal Inspiratory Pressure (SNIP, cm H_2O)	61.4 (25.7)	57.8 (25.1)	59.7 (25.4)
Qualifying Weaker Hand Fatigue to 60% of Sub-Maximal Target (sec)	84.5 (49.1)	78.3 (50.4)	81.7 (49.7)

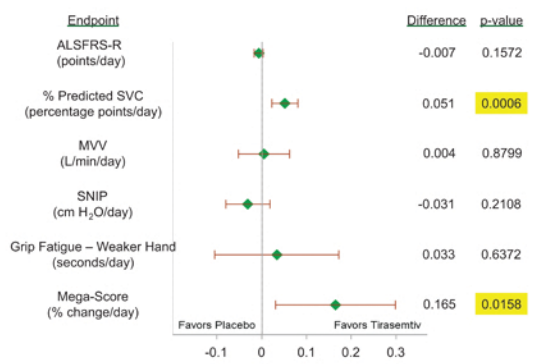
*p = 0.0125, *Tirasemtiv* vs. placebo; all others NS

BENEFIT–ALS (contd.)

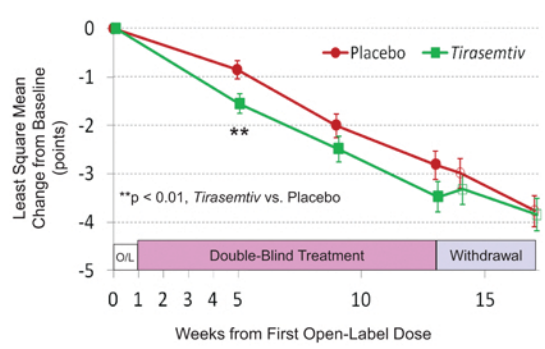
Dosing by Treatment Over Time



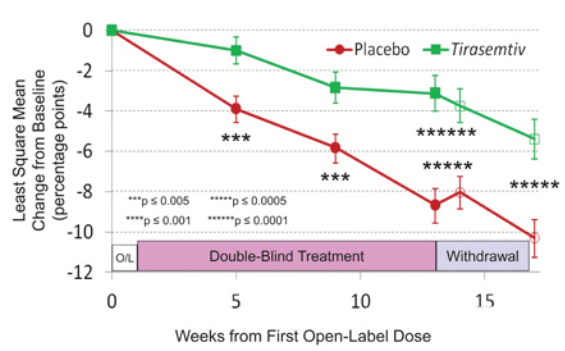
Slope of Change from Baseline to Week 12: Differences between *Tirasemtiv* and Placebo



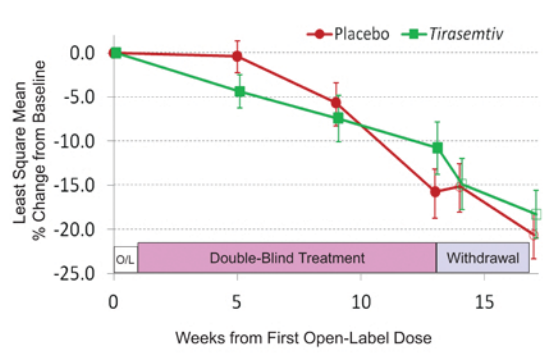
ALSFRS-R



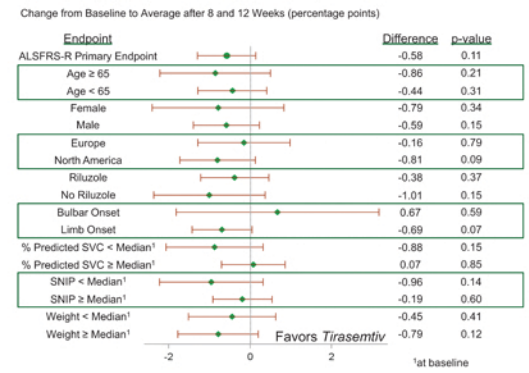
Slow Vital Capacity (% Predicted)



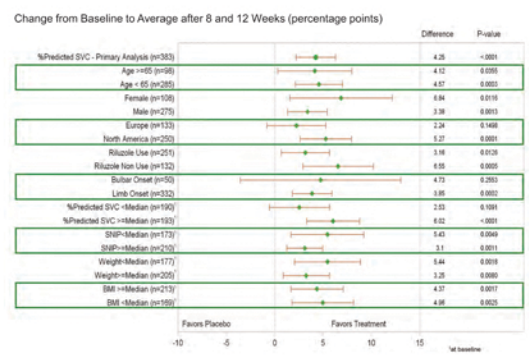
Muscle Strength Mega-Score (All Qualifying Muscle Groups, Including Hand Grip)



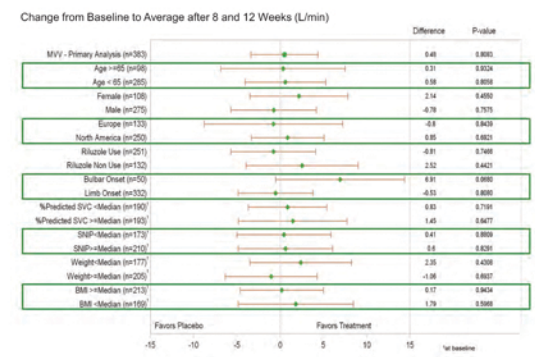
ALSFRS-R Primary Endpoint Change by Subgroup



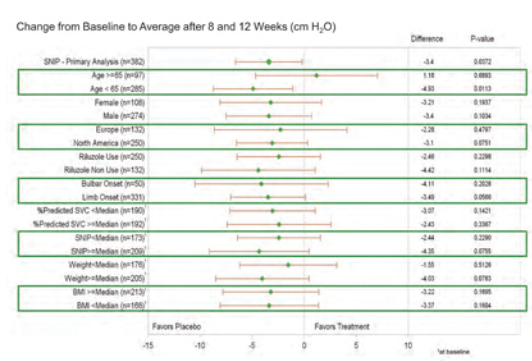
% Predicted SVC by Subgroup



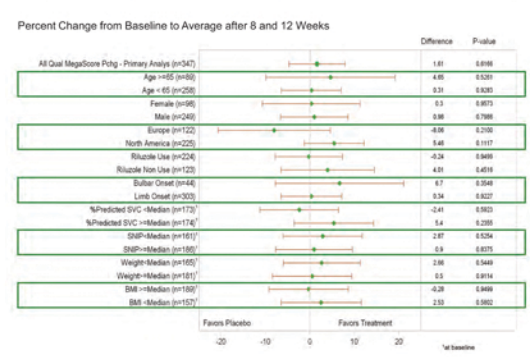
MVV by Subgroup



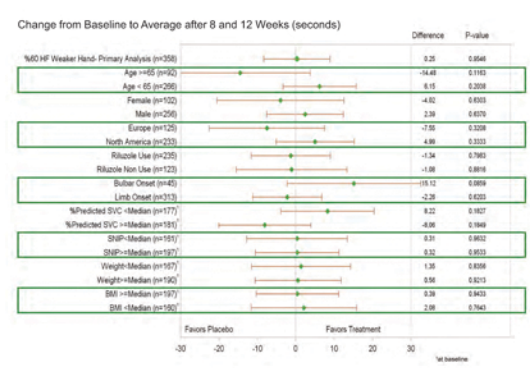
SNIP by Subgroup

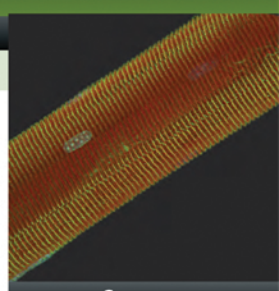


Mega-Score by Subgroup



Weaker Handgrip Fatigue by Subgroup





Summary

- The primary efficacy endpoint of BENEFIT-ALS (the change from baseline to the average of the ALSFRS-R total scores at Visits 6 and 7, after 8 and 12 weeks of double-blind treatment, respectively) was not statistically different between treatment groups
- Secondary endpoints included measures of respiratory function (SVC, MVV, SNIP) and other assessments of skeletal muscle performance (muscle strength Mega-Score, Handgrip Fatigue). Of these measures:
  - Treatment with *tirasemtiv* resulted in a statistically significant and potentially clinically meaningful slowing of the rate of decline of SVC versus placebo, which was present at each time point it was assessed. The difference in SVC versus placebo persisted for at least four weeks following *tirasemtiv* discontinuation
  - *Tirasemtiv* also slowed the decline in the muscle strength Mega-Score versus placebo
  - There was no statistically significant difference between treatment groups for the remaining secondary endpoints
- Subgroup analyses
  - SVC
    - *Tirasemtiv* reduced the decline in SVC compared to placebo by a similar magnitude regardless of age, gender, geographic region, *riluzole* use, site of ALS onset, baseline pulmonary function, and baseline weight and BMI
    - The reduced decline in SVC versus placebo was statistically significant within each subgroup examined except patients enrolled in Europe, those with bulbar onset, and those with a % predicted SVC < the median at baseline
  - *Tirasemtiv* had no effect on MVV in any subgroup examined; however, a trend toward an increase on *tirasemtiv* versus placebo in patients with bulbar onset approached statistical significance
  - Overall, SNIP was reduced on *tirasemtiv* versus placebo and the magnitude of this effect was similar across all subgroups except in patients older than 65 years, in whom a marginal increase was observed; conversely, the only subgroup in which the reduction on *tirasemtiv* versus placebo was statistically significant was in patients < 65 years old
  - *Tirasemtiv* had no effect on muscle strength or handgrip fatigue, neither overall nor within any of the subgroups examined

Conclusions

- *Tirasemtiv* may have both immediate and longer term pharmacologic effects, especially on SVC
- The potentially beneficial effects of *tirasemtiv* on measures of respiratory function and other assessments of skeletal muscle performance observed in BENEFIT-ALS merit further investigation

Cytokinetics