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Abstract

Objective: To assess the efficacy of *tirasemtiv*, a fast skeletal muscle troponin activator, vs. placebo in patients with amyotrophic lateral sclerosis. *Methods:* VITALITY-ALS (NCT02496767) was a multinational, double-blind, randomized, placebo-controlled clinical trial. Participants tolerating 2 weeks of open-label *tirasemtiv* (125 mg twice daily) were randomized 3:2:2:2 to placebo or one of three target *tirasemtiv* dose levels, using an escalating dosage protocol lasting 28 days. The primary outcome measure was changed in slow vital capacity (SVC) at 24 weeks. Secondary endpoints included a change in muscle strength and time to respiratory milestones of disease progression.

Results: Of 744 participants, 565 tolerated open-label *tirasemtiv* and received randomized treatment. By 24 weeks, 23 (12.2%) placebo-treated participants discontinued study treatment vs. 129 (34.2%) randomized to *tirasemtiv*. SVC declined by 14.4% (95% CI: -16.8, -11.9) in the placebo group and 13.4% (95% CI: -15.3, -11.6) in the *tirasemtiv* group (*p ¼* 0.56). Secondary endpoints did not show significant differences. However, participants who tolerated *tirasemtiv* at their randomized dose showed a numeric trend toward a dose-related slowing of decline in SVC (*p* = 0.11). Dizziness, fatigue, nausea, weight loss, and insomnia occurred more frequently on *tirasemtiv*. Serious adverse events were similar across groups.

Conclusions: Tirasemtiv did not alter the decline of SVC or significantly impact secondary outcome measures. Poor tolerability of *tirasemtiv* may have contributed to this result. However, participants tolerating their intended dose exhibited a trend toward treatment benefit on SVC, suggesting the underlying mechanism of action may still hold promise, as is being tested with a different fast skeletal muscle troponin activator (NCT03160898).

KEYWORDS: *Randomized clinical trial*, *amyotrophic lateral sclerosis*, *tirasemtiv*

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder causing progressive weakness and death, on average 3–5 years after diagnosis and most often as a result of respiratory failure (1–4).

Most therapeutic approaches to treating ALS have targeted neurodegeneration, although skeletal muscle is also a plausible target (5). *Tirasemtiv*, a fast skeletal muscle troponin activator (FSTA), increases skeletal muscle contractility by sensitizing the sarcomere to calcium (6,7). A large, multinational, randomized, double-blind, placebo-controlled, phase IIb clinical trial (BENEFIT-ALS) (8) randomized 605 participants with ALS who tolerated 1 week of open-label *tirasemtiv* 125 mg twice a day (BID). Participants randomized to *tirasemtiv* underwent weekly dose escalation to a maximum tolerated dose of 250 mg BID in the 12-week, double-blind phase of the study. No treatment effect was noted in the primary endpoint (change from baseline in ALS Functional Rating Scale-Revised [ALSFRS-R]). However, slow vital capacity (SVC) and muscle strength declined significantly more slowly in *tirasemtiv*-treated participants (8). *Tirasemtiv* reduced the slope of decline in SVC by ~50% during the 12-week treatment phase (9). Dizziness was the most commonly reported adverse event (AE) (8).

A phase III trial (VITALITY-ALS) was designed to extend and confirm the findings of BENEFIT-ALS. Double-blind treatment was extended to 48 weeks, with the primary outcome, change in SVC, evaluated at 24 weeks. To improve tolerability, the open-label period was extended to 2 weeks, and dose escalation occurred every 2 weeks rather than weekly. Three target dose levels were studied.

Methods

Participants

Adults with possible, probable, or definite ALS in accordance with the revised El Escorial criteria (10) were enrolled from 79 sites in 11 countries in North America and Europe. Inclusion criteria required an upright SVC 2:70% predicted for age, height, and sex. No participants were taking edaravone during this study, and prior exposure to *tirasemtiv* was exclusionary.

Standard protocol approvals, registrations, and patient consents

All participants in VITALITY-ALS provided written informed consent, and institutional review board approvals were received at all sites before enrollment. The study was conducted in accordance with the Declaration of Helsinki. An independent data and safety monitoring board monitored safety throughout the study. This study was registered with ClinicalTrials.gov (NCT02496767).

Study design

Following a screening period of up to 14 days, eligible participants were enrolled in the trial. The study included an open-label phase; a 48-week, double-blind, placebo-controlled phase; and then a 4-week, double-blind, placebo-controlled *tirasemtiv* withdrawal phase intended to assess for a potential rebound effect (none was observed, and not further discussed here). Participants who successfully completed 2 weeks of treatment with open-label *tirasemtiv* 125 mg BID were randomized (using a centralized IWRS system) 3:2:2:2 to matching placebo or one of three different target daily dose levels of *tirasemtiv* (250, 375, or 500 mg) stratified by riluzole use vs. nonuse. It was felt that patients who could not tolerate 125 mg BID as an initial dose would be unlikely to complete the study, so we did not titrate to this dose. All participants on riluzole took 50 mg daily from their personal supply in the morning and a blinded dose of riluzole in the evening in the same manner as in BENEFIT-ALS. All participants randomized to double-blind *tirasemtiv* continued at 250 mg/day (125 mg BID) for the first 2 weeks of double-blind treatment. Participants randomized to a target daily dosage of 375 mg (125 mg in the morning and 250 mg in the evening) or 500 mg (250 mg BID) of *tirasemtiv* had their dose adjusted in 125-mg increments every 2 weeks until the tar- get dose was reached or signs of intolerance emerged, in which case the dose was not escalated or was down-titrated to 250 mg daily of *tirasemtiv* or matching placebo as necessary due to AEs. This titration period was not included in the open-label phase, as differential drop out would have rendered the 3 groups unequal.

The safety analysis set consisted of all participants who received any dose of study drug. The full analysis set (FAS) included participants who received at least one dose of study medication during the randomized, double-blind, placebo-controlled phase and had at least one post-randomization efficacy assessment. There were a total of six post randomization assessments through 24 weeks. The per-protocol set (PPS) consisted of all participants who completed 2:20 weeks of double-blind, placebo-controlled treatment, had at least one post-randomization efficacy assessment on double-blind study treatment, and had no major protocol violations.

Assessments

The last assessment obtained before the first dose of the open-label phase was considered baseline. The primary endpoint was change in percent predicted SVC from baseline to week 24 of the double-blind, placebo-controlled phase. Secondary

endpoints included muscle strength assessed by hand-held dynamometry, the respiratory subscales of the ALSFRS-R, and time to certain respiratory milestones of disease progression, such as the initiation of assisted ventilation during the 48 weeks of randomized, double-blinded treatment. Safety assessments included physical examinations, clinical laboratory evaluations, vital signs, and monitoring of AEs and serious AEs (SAEs).

Statistical methods

The primary global null hypothesis was that no treatment difference existed in the change from baseline in percent predicted SVC at week 24 between participants in the FAS randomized to placebo and those randomized to *tirasemtiv* (pooled three-target dosage levels) during placebo-controlled, double-blind treatment. The original protocol sample size estimation indicated that ~360 participants were needed to complete the 24 weeks of double-blind treatment to provide 90% power to detect a treatment difference from placebo in percent predicted SVC change from baseline to the end of the first 24-week phase of 6% (an ~30% change from placebo) for all *tirasemtiv* target dose groups pooled using a common standard deviation of 17% with a two-tailed alpha of 0.05. Dropout rates of 16% at 24 weeks for placebo and 25% for all *tirasemtiv* target dose groups combined were assumed, necessitating ~600 participants enrolled in the study and rv477 participants randomized to placebo and the three different target dose levels of *tirasemtiv* in an allocation ratio of 3:2:2:2 in the double-blind, placebo-controlled treatment phase, stratifying based on riluzole use. The final sample size was slightly higher after adjusting for the aggregate blinded standard deviation and dropout rate during the study. Subjects withdrawing from active treatment were encouraged to attend all scheduled study visits and complete assessments and, if unable to attend, were contacted by phone on a monthly basis to obtain vital status and respiratory status through 48 weeks.

The primary analysis was performed using a repeated-measures mixed model with restricted maximum likelihood method (PROC MIXED default; SAS®, Cary, NC). The model included terms for treatment, baseline, pooled site, visit, and riluzole use/nonuse as well as interaction terms for treatment-by-visit and baseline-by-visit with an unstructured covariance matrix. Multiple imputation by randomized treatment dosage group was performed for missing data prior to modeling. The repeated-measures mixed model was applied to other change from baseline secondary endpoints. Cox regression models were used to estimate the hazard ratios of time to event endpoints between *tirasemtiv* and placebo, stratified by randomization strata.

Data availability statement

In collaboration with the ALS association, this study also included a biofluids collection at every visit. All demographic and efficacy data will be migrated to NeuroBANK, a database maintained by the NEALS Biorepository. Biofluids and phenotypic data will be available through application to the NEALS Biorepository Committee.

Results

Baseline characteristics

Of 866 participants screened, 744 were enrolled and 565 received randomized treatment (one patient was randomized but did not receive the treatment). After successfully completing the open-label phase, 188 patients received at least one dose of placebo and 377 received at least one dose of *tirasemtiv*. Demographics at study entry (Table 1) were similar to another recent phase III trials (8,11–15). The majority of participants (74.5% [554/744]) were taking riluzole at the start of the study. Baseline characteristics between riluzole and non-riluzole strata were similar.

Open-label phase

In the open-label phase of the study, 86.0% (640/ 744) of participants experienced AEs, most commonly dizziness (48.5% [361/744]), fatigue (27.4% [204/744]), and nausea (14.5% [108/744]). Only 1.5% (11/744) of participants (4 not taking and 7 taking riluzole) experienced SAEs; 23.7% (176/744) of participants discontinued from the study during the open-label phase, with a similar discontinuation rate among participants taking riluzole (26.7% [148/554]) and those not taking riluzole (31.1% [59/190]) (Figure 1). AEs were the most common reason for discontinuation, with 11.6% of participants (86/744) discontinuing because of dizziness, 8.1% (60/744) because of fatigue, and 4.2% (31/744) because of nausea. Riluzole did not significantly affect the frequency or type of AE resulting in discontinuation. The baseline demographics and disease characteristics of participants completing the open-label phase and randomized into the double-blind, placebo- controlled phase were similar to those at the time of entry into the open-label phase (Table 1).

Double-blind, placebo-controlled phase

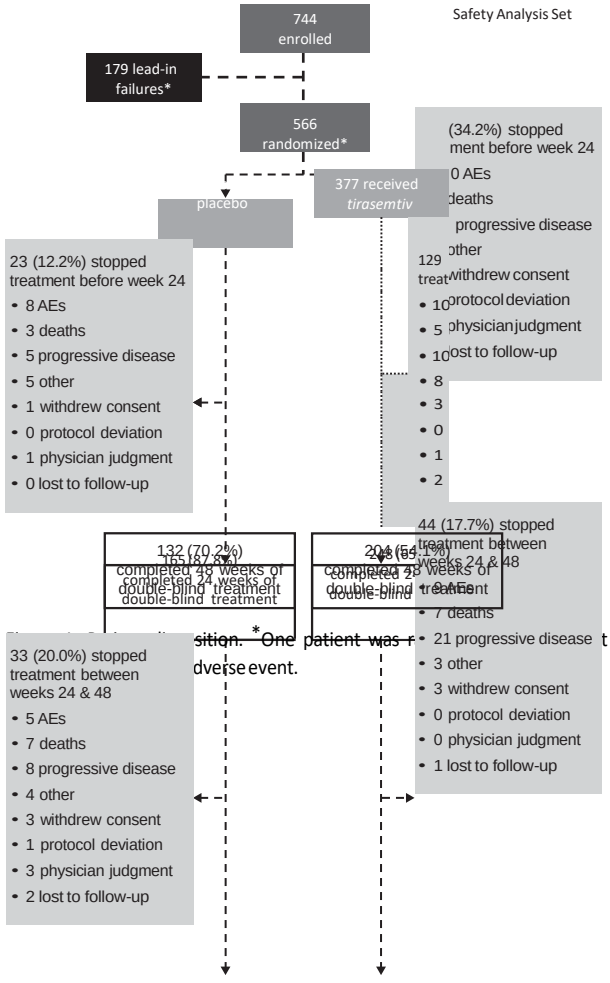
Participant disposition is shown in Figure 1. Overall, 183 participants were randomized to placebo; 165 (87.8%) completed 24 weeks of treatment, and 177 (94.1%) completed the week 24 visit. In contrast, 248 (65.8%) participants randomized to *tirasemtiv* completed 24 weeks of treatment and 311 (82.5%) completed the week 24 visit. There were 97 (77.0%), 60 (47.6%), and 39 (31.2%) patients who tolerated and achieved their randomized target doses of 250 mg/day, 375mg/day, and 500mg/day at week 24, respectively. AEs were the most common reason for discontinuing therapy and were more common in participants randomized to *tirasemtiv*. Termination from treatment primarily occurred during the first 12 weeks and in relation to dose titration (Figure 2); the frequency of study drug discontinuation was strongly related to the target dosage level. Down-titrations also occurred early but were not effective in deterring study drug discontinuation. Following 12 weeks of treatment with the study drug, participants on placebo and on *tirasemtiv* stopped treatment at similar rates (Figure 2). AEs and SAEs are shown in Table 2 and Table 3, respectively; the AE profile was similar to the previously reported phase II trial. Rates of SAEs and deaths were not different between *tirasemtiv*- and placebo-treated groups. Seventeen patients died during active treatment on placebo [9.0%] as compared with 26 deaths during active treatment on *tirasemtiv* [6.9%] after >1 year of exposure to study medication. At 24 weeks, there was no significant difference in the decline in percent predicted SVC in the placebo-treated group compared with all *tirasemtiv*-treated participants (14.4% for placebo, 13.4% for all *tirasemtiv*; p¼0.56). Decline in percent predicted SVC was 12.6% for the 250-mg target dose group, 13.7% for the 375-mg target dose group, and 13.9% for the 500-mg target dose group (p¼0.38, 0.76, and 0.84, respectively). There was no significant difference between placebo and all *tirasemtiv*-treated participants on the following secondary endpoints: ALSFRS-R respiratory domain score change from baseline to week 48, slope of Muscle Strength Mega-Score from baseline to week 48, time to the first occurrence of a decline from baseline in percent predicted SVC 2:20 percentage points or the onset of respiratory insufficiency or death to week 48, time to the first occurrence of a decline in SVC >50% predicted or the onset of respiratory insufficiency or death over 48 weeks, change from baseline in the ALSFRS-R total score to the end of week 48, and time to first use of mechanical ventilator assistance or death to week 48 (p=0.92, 0.75, 0.46, 0.76, 0.61, 0.65, respectively).

To assess whether a potential benefit of *tirasemtiv* was masked by poor tolerability, two separate analyses were performed on more restrictive data sets. The PPS included participants who completed 2:20 weeks of study medication and contributed outcome measures at the 24-week time point, when the primary outcome measure was assessed. It eliminated participants who had stopped study medication for >4 weeks and includes no imputations for missing data. However, participants who reduced their dose were still included within their target dose group. In this data set, the point estimate of effect was greater than for the FAS; for the 250-mg target dosage group in the PPS, percent predicted SVC declined by 10.0 percentage points, compared with 13.1 percentage points for the placebo group (Table 4). This difference was not statistically significant (p = 0.13), and there was an inverse dose-response similar to the primary analysis, with participants randomized to higher dosage groups performing less well than the 250-mg target dosage group.

Table 1. Demographics and baseline disease characteristics.

Parameters	Safetyanalysisset Enrolled (*n* 5744)	Full analysis set Placebo (*n* 5 188)	Full analysis set All *tirasemtiv* (*n* 5 373)	*p* value
Age, y, mean (SD)	57.6 (10.3)	55.9 (10.6)	56.8 (10.0)	0.29
Age <65 y, *n* (%)	541 (72.7)	143 (76.1)	291 (78.0)	0.61
Male, *n* (%)	485 (65.2)	123 (65.4)	263 (70.5)	0.30
Riluzoleuser, *n* (%)	554 (74.5)	141 (75.0)	281 (75.3)	0.84
Weight, kg, mean (SD)	79.3 (15.4)	80.7 (15.7)	81.1 (14.8)	0.71
BMI, kg/m^2, mean (SD)	26.9 (4.2)	27.3 (4.3)	27.2 (4.1)	0.81
Months from diagnosis, mean (SD)	7.7 (5.8)	8.1 (6.0)	7.4 (5.6)	0.19
Months from first symptom, mean (SD)	20.7 (13.8)	21.5 (16.2)	20.0 (12.9)	0.39
Bulbar onset, *n* (%)	112 (15.1)	31 (16.5)	54 (14.5)	0.53
ALSFRS-Rtotalscore, mean (SD)	38.1 (5.1)	38.3 (5.1)	38.1 (5.3)	0.68
ALSFRS-R respiratory domain score, mean (SD)	11.5 (0.9)	11.6 (0.8)	11.5 (0.9)	0.23
SVC (% predicted), mean (SD)	90.7 (15.7)	90.7 (16.5)	90.4 (15.3)	0.85

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI: body mass index; SD: standard deviation; SVC: slow vital capacity.



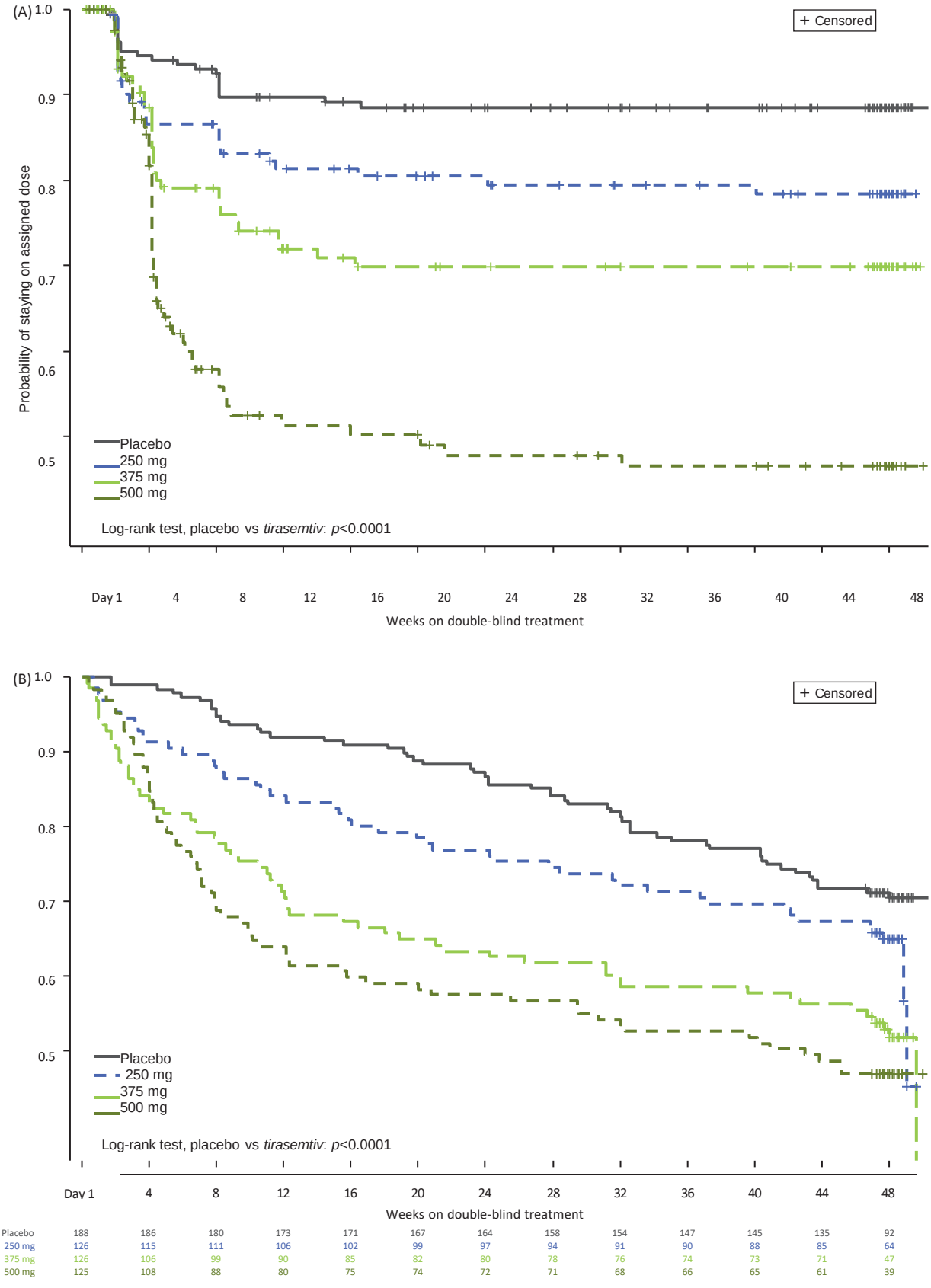


Figure 2. Probability of (A) staying on the assigned treatment dose and (B) staying on treatment.

Table 2. Most common TEAEs during the 48-week, double-blind, placebo-controlled phase.

Preferred term, *n* (%)	All participants (*N* 5 565)	Placebo (*n* 5 188)	All *tirasemtiv* (*n* 5 377)	Difference (%)
Patients with at least 1 TEAE	557	182 (96.8)	375 (99.5)	2.7
Fatigue	208	61(32.4)	147 (39.0)	6.6
Dizziness	203	45(23.9)	158 (41.9)	18
Muscular weakness	186	58(30.9)	128 (34.0)	3.1
Weight decreased	150	40(21.3)	110 (29.2)	7.9
Nausea	114	30(16.0)	84(22.3)	6.3
Constipation	112	40(21.3)	72(19.1)	-2.2
Insomnia	103	25(13.3)	78(20.7)	7.4
Dysphagia	99	33(17.6)	66(17.5)	-0.1
Dyspnea	92	35(18.6)	57(15.1)	-3.5
Muscle spasms	92	34(18.1)	58(15.4)	-2.7
Contusion	90	34(18.1)	56(14.9)	-3.2
Nasopharyngitis	81	30(16.0)	51(13.5)	-2.5
Headache	81	28(14.9)	53(14.1)	-0.8
Asthenia	78	22(11.7)	56(14.9)	3.2
Depression	77	22(11.7)	55(14.6)	2.9
Decreased appetite	75	19(10.1)	56(14.9)	4.8
Somnolence	70	14 (7.4)	56(14.9)	7.5
Anxiety	70	19(10.1)	51(13.5)	3.4
Skin abrasion	65	24(12.8)	41(10.9)	-1.9
Post traumatic pain	64	26(13.8)	38(10.1)	-3.7

TEAE: treatment-emergent adverse event.

Table 3. Serious AEs occurring in >1% of participants during the 48-week double-blind phase.

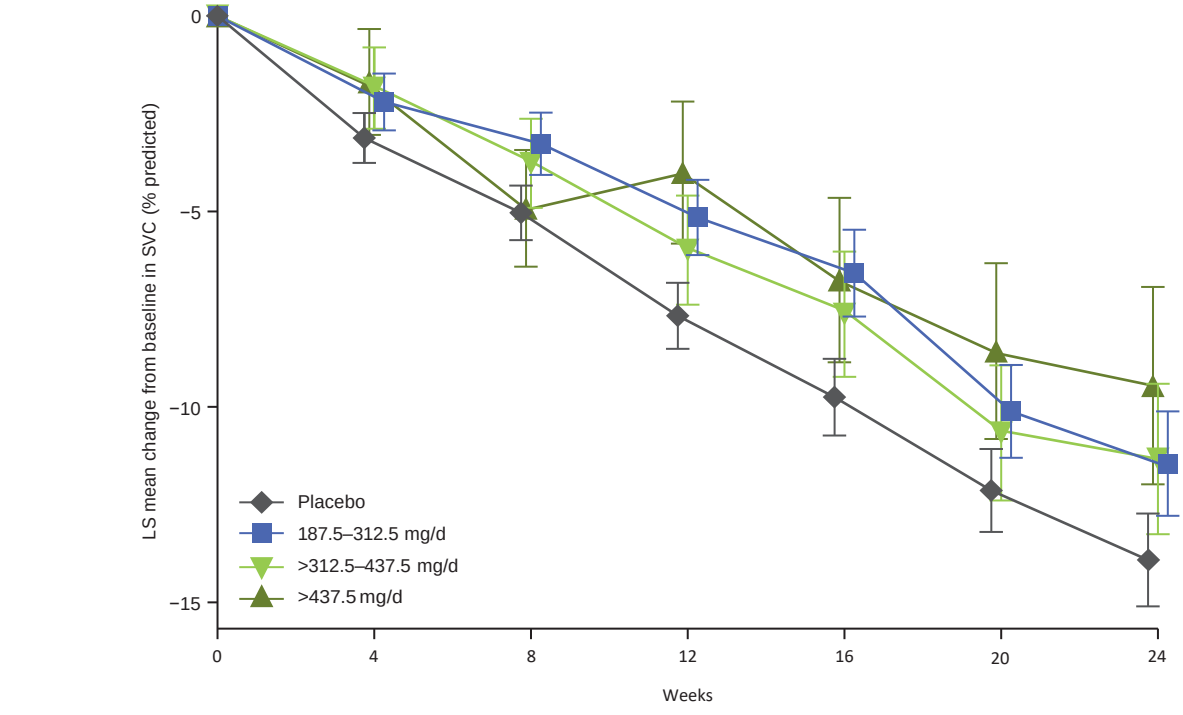
Preferred term, *n* (%)	Placebo (*n* 5 188)	All *tirasemtiv* (*n* 5 377)	Overall (*N* 5 565)
Patients with serious AEs	53(28.2)	92(24.4)	145 (25.7)
Dysphagia	9(4.79)	21(5.57)	30(5.31)
Respiratory failure	8(4.26)	17(4.51)	25(4.42)
Decreased weight	2(1.06)	10(2.65)	12(2.12)
Amyotrophic lateral sclerosis	4(2.13)	6(1.59)	10(1.77)
Pneumonia	4(2.13)	4(1.06)	8(1.42)
Pneumonia aspiration	4(2.13)	2(0.53)	6(1.06)
Traumatic fracture	4(2.13)	2(0.53)	6(1.06)

AE: adverse event.

Table 4. Percent predicted SVC change from baseline to week 24 in PPS, mixed model for repeated measures.

	Placebo	*Tirasemtiv* overall	*Tirasemtiv* 250 mg	*Tirasemtiv* 375 mg	*Tirasemtiv* 500 mg
Patients in PPS, *n*	157	239	91	79	69
LS means (SE)	-13.1 (1.26)	-10.9 (1.03)	-10.0 (1.64)	-10.7 (1.75)	-12.4 (1.89)
LS means from placebo (95% CI)		2.2 (-0.95, 5.31)	3.1 (-0.92, 7.10)	2.4 (-1.82, 6.58)	0.8 (-3.66, 5.16)
p value		0.1715	0.1310	0.2656	0.7387

CI: confidence interval; LS: least squares; PPS: per-protocol set; SE: standard error; SVC: slow vital capacity.



Number of patients on study medication

Placebo	188	186	169
187.5–312.5 mg/d	126	146	140
>312.5–437.5 mg/d	125	68	67
>437.5 mg/d	122	40	40

Change in SVC week 24	Placebo	187.5–312.5 mg/d	>312.5–437.5 mg/d	>437.5 mg/d
LS mean (percentage points)	−14.2	−11.7	−11.6	−9.7
LS mean difference from placebo (percentage points)		2.6	2.7	4.6
P value		0.160	0.247	0.107

Figure 3. Change from baseline in percent predicted SVC in patients completing 24 weeks of treatment. Error bars represent standard error of the mean. LS: least squares; SVC: slow vital capacity.

A second analysis evaluated whether participants who tolerated their target dose level well enough to stay at the target dose showed a greater positive impact of *tirasemtiv.* Change in SVC was evaluated as a function of average daily maintenance dosage from the end of week 8 for dose titration to the end of week 24. In this analysis, all patients who remained on study drug through 24 weeks were included. The greatest estimate of effect was noted in participants randomized to the highest daily dosage (500 mg) who were able to tolerate study drug at that dose (Figure 3).

Participants in this group showed a decline in per- cent predicted SVC of 9.7 percentage points compared with a drop of 14.2 percentage points in placebo-treated participants (p=0.11). This difference represents a 32% slower decline in SVC for those treated with *tirasemtiv* at a daily dosage of 500 mg compared with placebo treatment; if this point estimate was a true effect of *tirasemtiv* in participants who tolerated this dose, such a difference likely would be clinically important. Every 100 mg of daily *tirasemtiv* was associated with a 0.19-percentage point (p = 0.019) improvement in change from baseline of percent predicted SVC per month. This analysis suggested that there was an expected dose response for those patients who were able to tolerate *tirasemtiv* at their assigned target dosage level, such that participants receiving lower dosages experienced less of an effect than those receiving higher dosages of *tirasemtiv.* No treatment effect was observed on ALSFRS-R and hand-held dynamometry endpoints. When the baseline characteristics of patients who remained on double-blind treatment (whether at their target doses or after down-titration) were compared to those who did not, those who discontinued double-blind treatment were, on average, slightly older, had lower vital capacities and ALSFRS-R total scores (and were less likely to be scored as 4 on the dyspnea and orthopnea domains), were less likely to be on riluzole, and were more likely to use caffeine.

Discussion

In the primary analysis of the FAS, no significant differences were seen in the primary outcome measure or any secondary measures comparing all *tirasemtiv*-treated participants with placebo-treated participants. There appeared to be an inverse dose-response relationship with respect to the primary outcome measure. However, this is likely spurious, as many higher-dosage participants had been reduced to the lowest dose, and more had also stopped study drug at higher dosages but remained in the study providing outcome measure data without receiving therapy.

Results demonstrated that tolerability was not improved by the dosing strategies used in this study, indicating that overall tolerability was dose-dependent and not strongly improved by a slower dose escalation. A slightly higher percentage of participants withdrew during the open-label phase as compared with BENEFIT-ALS. However, of those who were randomized and continued into the double-blind phase, approximately the same percentage of participants stopped study drug by 12 weeks as compared with BENEFIT-ALS by 12 weeks. In both studies, study drug discontinuation occurred early, usually within 1 week of dose escalation. Dose reductions also occurred early in VITALITY-ALS but did not improve retention. Participants who were randomized to higher dos- ages but were down-titrated to 125 mg BID were much more likely to ultimately stop study drug than those originally randomized to the same dosage. Participants on *tirasemtiv* also experienced more AEs, most notably dizziness, fatigue, and nausea. Importantly, however, there was no increase in SAE rates in patients on active treatment and no indication of increased mortality.

Despite the impact of poor tolerability on the results of this study, 2 analyses prespecified in the protocol suggested a benefit in patients able to tolerate *tirasemtiv.* In the PPS, participants who were randomized to the 250-mg target daily dose group of *tirasemtiv* declined in SVC 24% more slowly than those on placebo (Table 4). This change, if true, would be clinically important; the fact that the difference between active treatment and placebo was smaller than in BENEFIT-ALS may be partially explained by the fact that the cohort as a whole declined more slowly than expected (dis- cussed below). The observation that the lower dos- ages were associated with larger treatment differences was consistent with the inverse dose- response relationship in tolerability among randomized dosage groups. However, when participants were evaluated according to the maintenance dose from the end of week 8 to the end of week 24, those who tolerated the highest average daily dosage (~500 mg of *tirasemtiv* daily), showed an SVC decline that was 32% slower than those on placebo in the FAS, with a positive dose- response relationship. Overall, the poor tolerability of *tirasemtiv* appears to have masked the potential treatment benefit with regard to SVC. These results suggest that the underlying mechanism of action of *tirasemtiv* still has promise in patients with ALS.

This study did not meet its primary endpoint. Although there was a trend toward benefit in *tirasemtiv*-treated participants, it was not statistically significant and not considered clinically meaningful. There are several reasons why a potential positive effect was obscured in this study. First, as discussed above, tolerability was a significant issue, with >50% more patients stopping study drug on active treatment as compared with placebo. When patients who tolerated *tirasemtiv* were evaluated separately, much larger and potentially important estimates of effect were seen. These effects did not reach statistical significance at least in part because of the small sample sizes in these groups. Secondly, participants recruited to this study per- formed differently than other recent ALS cohorts, at least with regard to SVC rate of change. The decline in SVC was lower than expected. Over 24 weeks, the decline in SVC was 14.2% or 0.080% per day in the placebo group for VITALITY-ALS. For comparison, the rate of decline for placebo-treated ALS patients in the phase III trial of dexpramipexole was 0.088% per day or 16.9% over 24 weeks and 0.090% per day for the phase II trial of *tirasemtiv*. The slower progression rate in the current study may have contributed to the finding of no significant treatment effect. However, as was noted in the phase 2 study (BENEFIT ALS), SVC was the measure that seemed to show the largest signal among all outcome measures, confirming that the choice in primary outcome measure was justified.

Thus, although this phase III study failed to show a meaningful effect of *tirasemtiv* on SVC, subanalyses suggest that *tirasemtiv* had a biological effect on SVC, such that fast skeletal muscle troponin activation remains worthy of further study. A next-generation FSTA (*reldesemtiv*), lacking central nervous system effects and having the potential to produce a larger pharmacodynamic effect (16), has been reported to show promising effects in spinal muscular atrophy (17) and is being tested in a large phase II trial in ALS patients (NCT03160898).

Declaration of interest

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