CLT-22

Impact of Time Since Diagnosis on Response to *Tirasemtiv*, A Fast Skeletal Muscle Troponin Activator, in Patients With Amyotrophic Lateral Sclerosis: A Subgroup Analysis of VITALITY-ALS

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INTRODUCTION

- Targeting skeletal muscle directly with a fast skeletal muscle troponin activator (FSTA) is one approach to the treatment of amyotrophic lateral sclerosis (ALS)
- *Tirasemtiv*, a first-in-class FSTA, has been shown to increase submaximal muscle force in the tibialis anterior of healthy volunteers[1]
- A phase 2b trial (BENEFIT-ALS) in patients with ALS demonstrated that 12 weeks of treatment with *tirasemtiv* preserved slow vital capacity (SVC) and muscle strength, although the primary endpoint (change in revised ALS Functional Rating Scale [ALSFRS-R] total score) was not met[2]
- A phase 3 multinational, double-blind, randomized, placebo-controlled, parallel-group study (VITALITY-ALS) was performed to evaluate the efficacy and safety of *tirasemtiv* in patients with ALS over a longer treatment period

OBJECTIVE

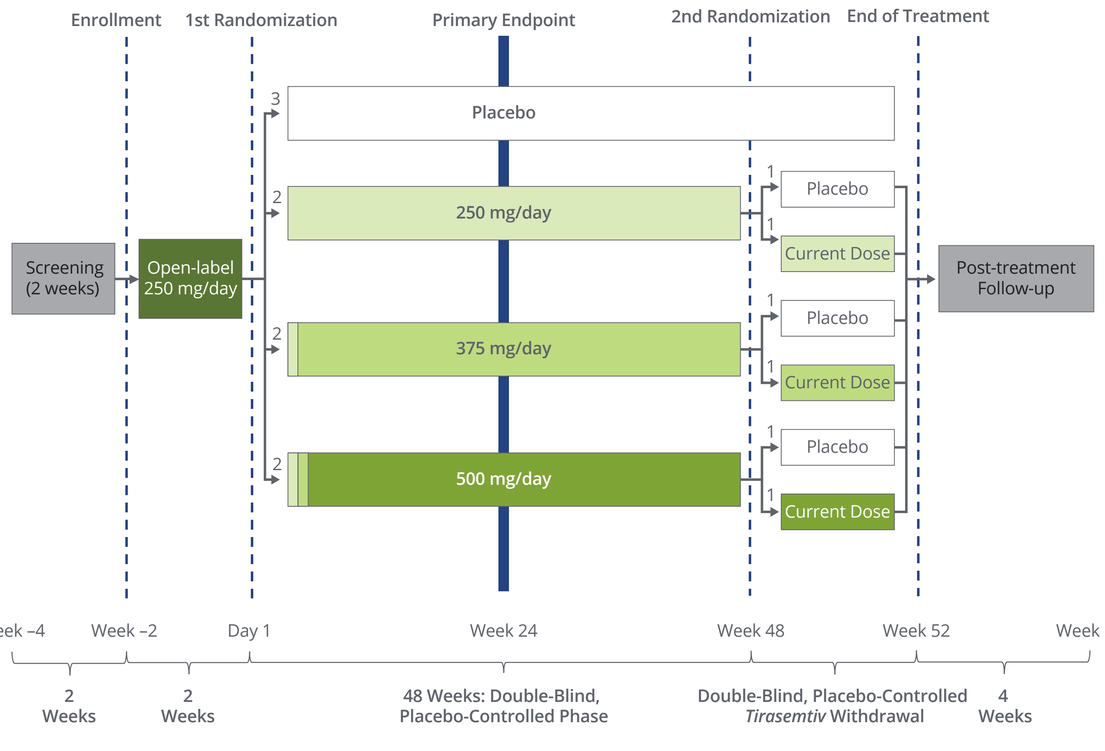
- This prespecified subgroup analysis of VITALITY-ALS assessed the impact of time from diagnosis on *tirasemtiv* efficacy in patients with ALS

METHODS

VITALITY-ALS

- Participants who tolerated 2 weeks of open-label *tirasemtiv* (125 mg twice a day) were randomized 3:2:2:2 to placebo or 1 of 3 target total doses of *tirasemtiv* (250, 375, or 500 mg/day; **Figure 1**)
- The dose was escalated every 2 weeks to the target daily dose or to the maximum tolerated dose. A single down-titration was allowed as necessary

Figure 1. Study schematic



Population:

- Eligible participants had a diagnosis ≤24 months and SVC ≥70% predicted
- Predefined subgroup analyses included time from ALS diagnosis (<median, ≥median; <1 year, ≥1 year)

Primary Endpoint:

- Change from baseline in percent predicted SVC at 24 weeks

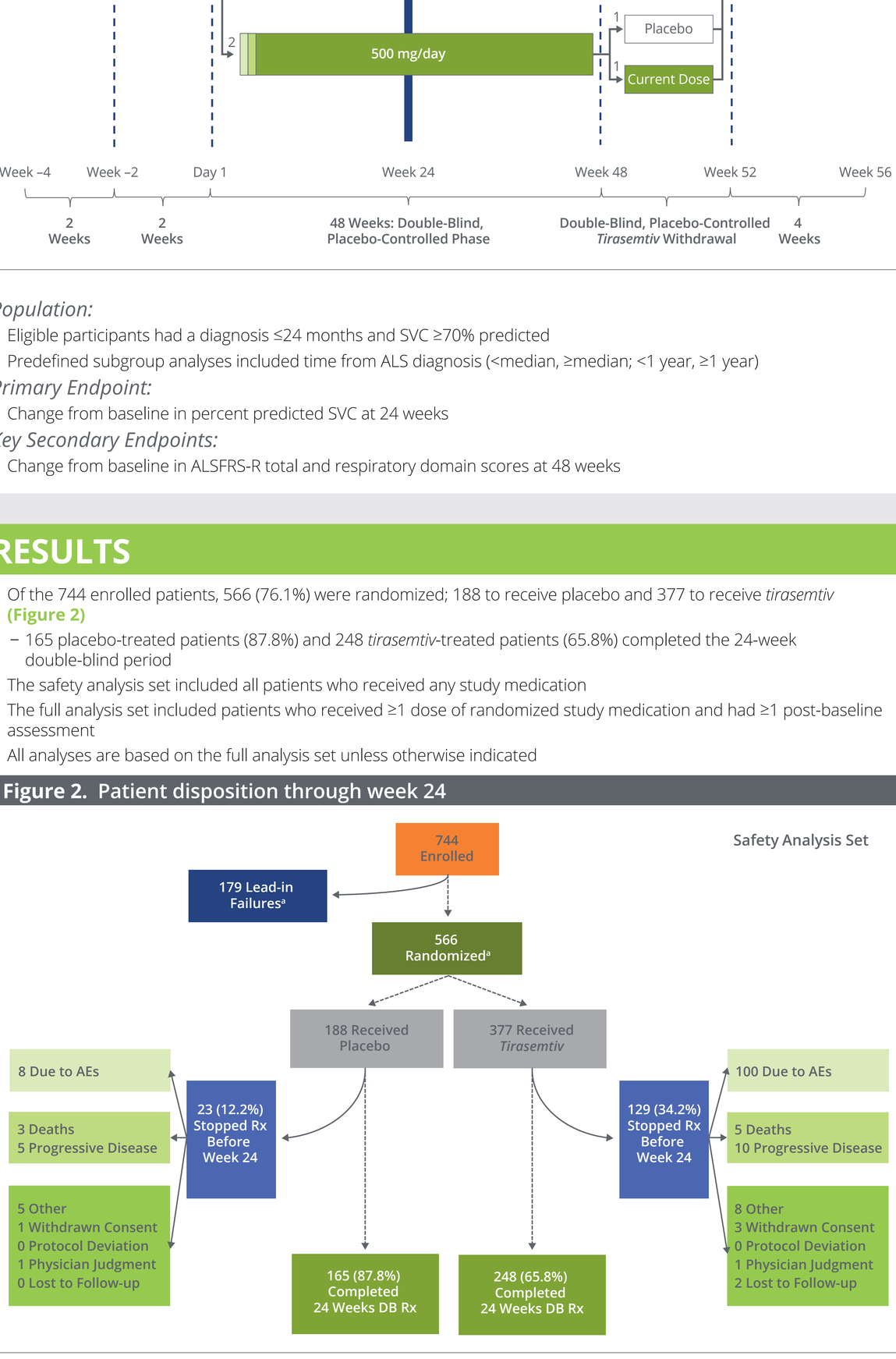
Key Secondary Endpoints:

- Change from baseline in ALSFRS-R total and respiratory domain scores at 48 weeks

RESULTS

- Of the 744 enrolled patients, 566 (76.1%) were randomized; 188 to receive placebo and 377 to receive *tirasemtiv* **(Figure 2)**
  - 165 placebo-treated patients (87.8%) and 248 *tirasemtiv*-treated patients (65.8%) completed the 24-week double-blind period
- The safety analysis set included all patients who received any study medication
- The full analysis set included patients who received ≥1 dose of randomized study medication and had ≥1 post-baseline assessment
- All analyses are based on the full analysis set unless otherwise indicated

Figure 2. Patient disposition through week 24



[a]Includes 1 Randomized to placebo in error as patient not tolerant to open-label lead-in drug and did not receive DB Rx
AE, adverse event; DB, double-blind; Rx, treatment

- Baseline demographics and disease characteristics were similar between treatment groups **(Table 1)**
- The median time from diagnosis across both groups was 6.1 months

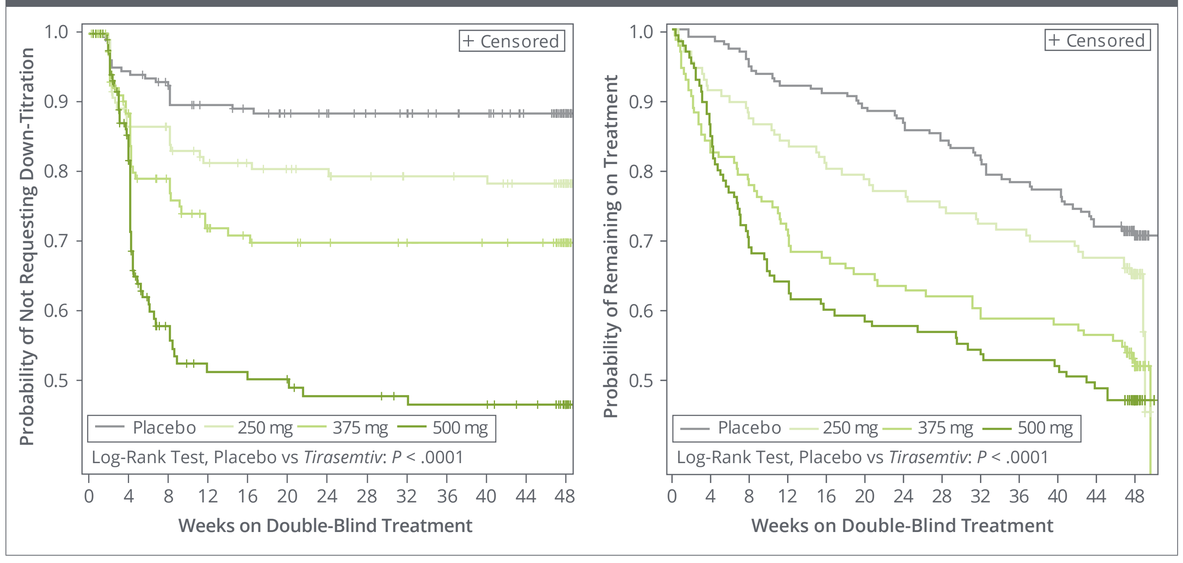
Table 1. Baseline demographics and disease characteristics (FAS)

Demographic	Placebo (n = 188)	All *Tirasemtiv* (n = 373)	*P* Value
Age, y, mean (SD)	55.9 (10.6)	56.8 (10.0)	.29
Age <65, y, n (%)	143 (76.1)	291 (78.0)	.61
Male, n (%)	123 (65.4)	263 (70.5)	.30
Riluzole user, n (%)	141 (75.0)	281 (75.3)	.84
Weight, kg, mean (SD)	80.7 (15.7)	81.1 (14.8)	.71
BMI, kg/m^2, mean (SD)	27.3 (4.3)	27.2 (4.1)	.81
Months from diagnosis, mean (SD)	8.1 (6.0)	7.4 (5.6)	.19
Months from first symptom, mean (SD)	21.5 (16.2)	20.0 (12.9)	.39
Bulbar onset, n (%)	31 (16.5)	54 (14.5)	.53
ALSFRS-R total score, mean (SD)	38.3 (5.1)	38.1 (5.3)	.68
ALSFRS-R respiratory domain score, mean (SD)	11.6 (0.8)	11.5 (0.9)	.23
SVC, % predicted, mean (SD)	90.7 (16.5)	90.4 (15.3)	.85

ALSFRS-R, revised ALS Functional Rating Scale; BMI, body mass index; FAS, full analysis set; SD, standard deviation; SVC, slow vital capacity

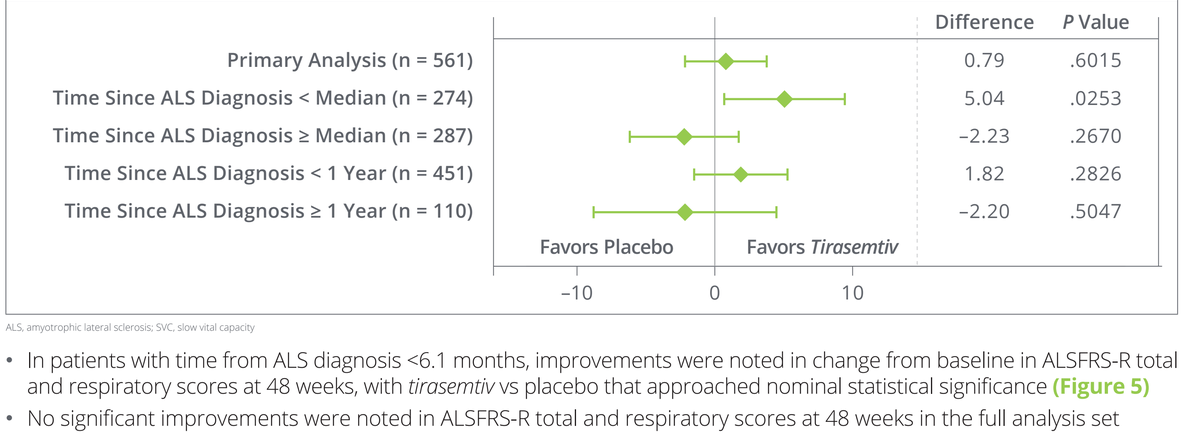
- The times to down-titration and early treatment termination are shown in **Figure 3**

Figure 3. VITALITY-ALS: (A) time to down-titration of study drug dose, and (B) time to early termination from treatment



- In the primary analysis (N = 561), there was no significant difference in change from baseline in percent predicted SVC at 24 weeks between *tirasemtiv*-treated (all doses combined) and placebo-treated patients (least squares [LS] mean difference: 0.79; *P* = .6015 vs placebo; **Figure 4**)
- In patients with a time from ALS diagnosis <6.1 months (n = 274), the change from baseline in percent predicted SVC significantly favored *tirasemtiv* vs placebo at 24 weeks (LS mean difference: 5.04; *P* = .0253 vs placebo)
- The change from baseline in percent predicted SVC was not significantly different in patients with a time from diagnosis of ≥6.1 months (n = 287), <1 year (n = 451), or ≥1 year (n = 110)

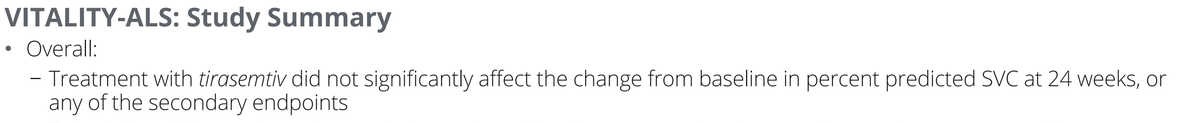
Figure 4. Change from baseline to Week 24 in percent predicted SVC in patients treated with *tirasemtiv* compared with placebo



ALS, amyotrophic lateral sclerosis; SVC, slow vital capacity

- In patients with time from ALS diagnosis <6.1 months, improvements were noted in change from baseline in ALSFRS-R total and respiratory scores at 48 weeks, with *tirasemtiv* vs placebo that approached nominal statistical significance **(Figure 5)**
- No significant improvements were noted in ALSFRS-R total and respiratory scores at 48 weeks in the full analysis set

Figure 5. Changes from baseline to Week 48 in ALSFRS-R total and respiratory scores among patients with time from ALS diagnosis <6.1 months



ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS Functional Rating Scale

VITALITY-ALS: Study Summary

- Overall:
  - Treatment with *tirasemtiv* did not significantly affect the change from baseline in percent predicted SVC at 24 weeks, or any of the secondary endpoints
  - Tolerability of *tirasemtiv* was inversely dose-related, leading to excessive dropouts from active treatment driven especially by patients randomized to the 2 higher target doses
- Patients with a time since ALS diagnosis less than the median at baseline (6.1 months) had better outcomes with *tirasemtiv* versus placebo in the following assessments measured in this study
  - SVC
  - ALSFRS-R total score
  - ALSFRS-R respiratory subscore

CONCLUSIONS

- **Results from this subgroup analysis of VITALITY-ALS suggest better outcomes with *tirasemtiv* in ALS patients with a shorter time since disease diagnosis**
- **Future studies in ALS may consider a shorter allowable time since ALS diagnosis (eg, 1 year instead of 2)**

References

1. Hansen R, et al. *Muscle Nerve.* 2014;50:925–31.
2. Shefner JM, et al. *Amyotroph Lateral Scler Frontotemporal Degener.* 2016;17:426–35.

Disclosures

Wolff, **Cockroft**, **Malik**, **Meng**, and **Rudnicki** are employees of and own stock in Cytokinetics, Inc. **Shefner** has consulted for Biogen, Biohaven, Cytokinetics, Inc., Mitsubishi Tanabe Pharma, and Neurosense, and has received research support from ALS Association, ALS Finding a Cure, Biogen, Biohaven, Cytokinetics, Inc., Neuraltus, and NIH.

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