

Effect of an Oral, Fixed-Dose Combination of Sodium Phenylbutyrate and Taurursodiol on Long-Term Tracheostomy/Ventilation-Free Survival and Hospitalization in Amyotrophic Lateral Sclerosis: Final Results From CENTAUR

Code: C0202



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INTRODUCTION

- Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disorder that typically culminates in death from respiratory failure^{1,2}
- Noninvasive ventilation or tracheostomy and invasive ventilation may prolong survival and maintain or enhance quality of life in people living with ALS^{1,3}
- Assisted ventilation and hospitalization are substantial drivers of aggregate annual costs and overall health burden in ALS⁴⁻⁶
- Therapies that slow disease progression have the potential to reduce short-term clinical burden in ALS⁷
- The safety and efficacy of an oral, fixed-dose combination of sodium phenylbutyrate and taurursodiol^a (PB and TURSO) was evaluated in the phase 2, multicenter, randomized, double-blind, placebo-controlled, CENTAUR trial in adults with ALS encompassing a 6-month randomized phase and an open-label extension (OLE) phase⁸
 - Treatment with PB and TURSO slowed functional decline, as indicated by the decrease in estimated mean rates of change of the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFERS-R) total score
 - PB and TURSO was generally well tolerated throughout the CENTAUR trial
 - Gastrointestinal adverse events occurred throughout but were reported more frequently in the PB and TURSO group and during the first 3 weeks of treatment⁸

^aAlso known as ursodocoltaurine.

OBJECTIVES

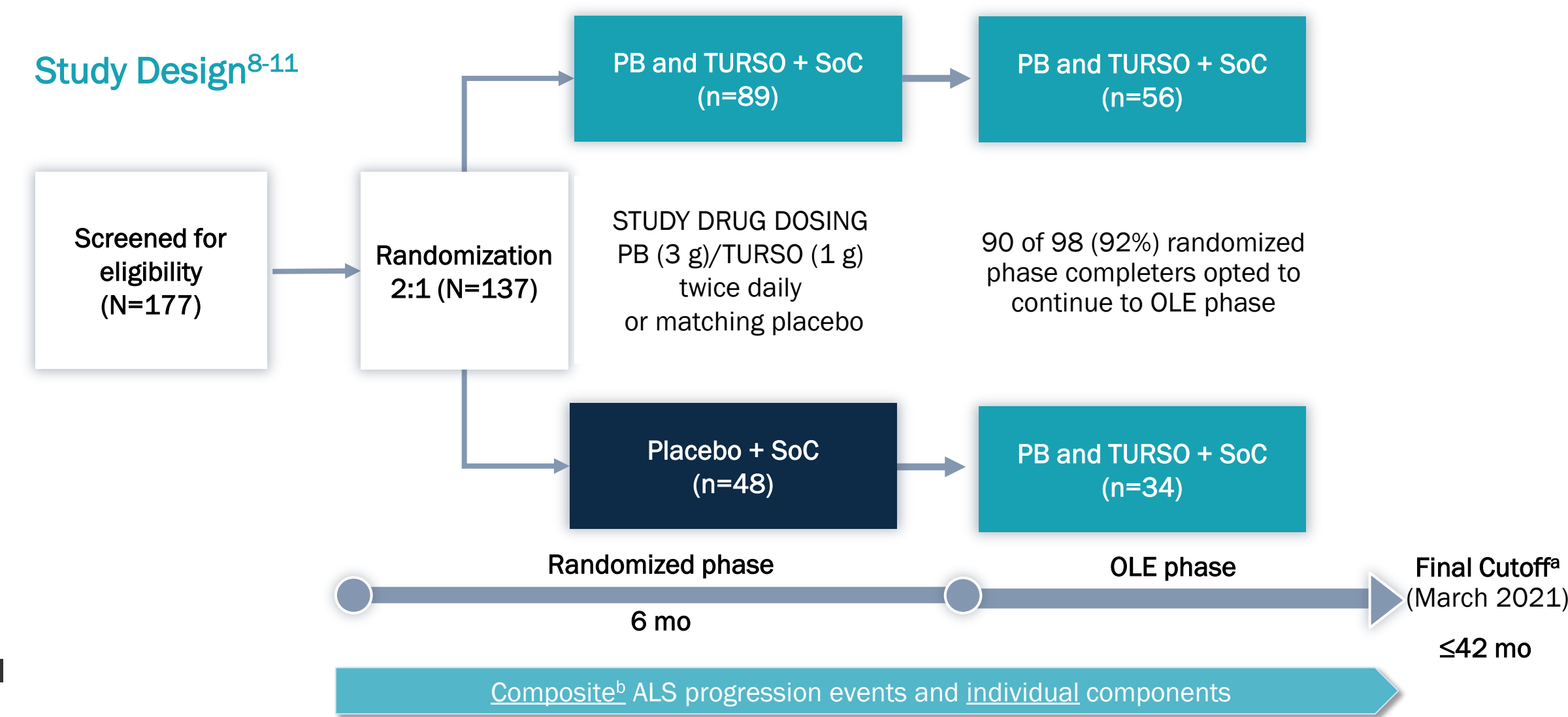
- Here, we report final analyses of ALS progression events in CENTAUR inclusive of the long-term, follow-up OLE phase, encompassing a postrandomization follow-up of ≤42 months
 - Analyses performed at an earlier timepoint have been previously published^{8,9}
 - These final analyses are from the end of the CENTAUR trial after the last participant completed the last visit of the OLE phase

METHODS

Outcome Measures

- Key ALS progression events (prespecified secondary end points) compared between participants originally randomized to PB and TURSO vs placebo (longest post-randomization follow-up, ≤42 months) were¹⁰:
 - Time to first hospitalization, death, or death equivalent
 - Time to all-cause death
 - Time to death or death equivalent (tracheostomy, permanent assisted ventilation [PAV])
 - Time to first hospitalization
- Vital status for participants (including those who discontinued, were lost to follow-up, or did not continue into the OLE phase) was ascertained by prospective monitoring or by the participant-locating service OmniTrace¹⁰
 - Vital status was successfully confirmed for all (134 of 135 participants) but 1 randomized participant in the modified intent-to-treat (mITT) population
- Other events were recorded prospectively via clinic reports

Study Design⁸⁻¹¹



Key inclusion criteria:

- Definite ALS, revised El Escorial criteria
- ≤18 mo from symptom onset
- Slow vital capacity >60%
- Riluzole/intravenous edaravone^c use permitted

SoC, standard of care.

^aAll randomized participants within this population were included in the analyses, including those who discontinued from the trial, were lost to follow-up, or did not continue into the OLE phase.

^bComposite includes death, tracheostomy/PAV, hospitalization.

^cOral edaravone was not approved at the time of the CENTAUR trial.¹²

Populations Analyzed

- A total of 135 participants in the mITT population were included in this analysis (original randomization: PB and TURSO, n=87; placebo, n=48)
- mITT population consisted of all randomized participants who received ≥1 dose of originally assigned trial medication and had ≥1 postbaseline ALSFRS-R total score¹⁰

Statistical Analysis¹⁰

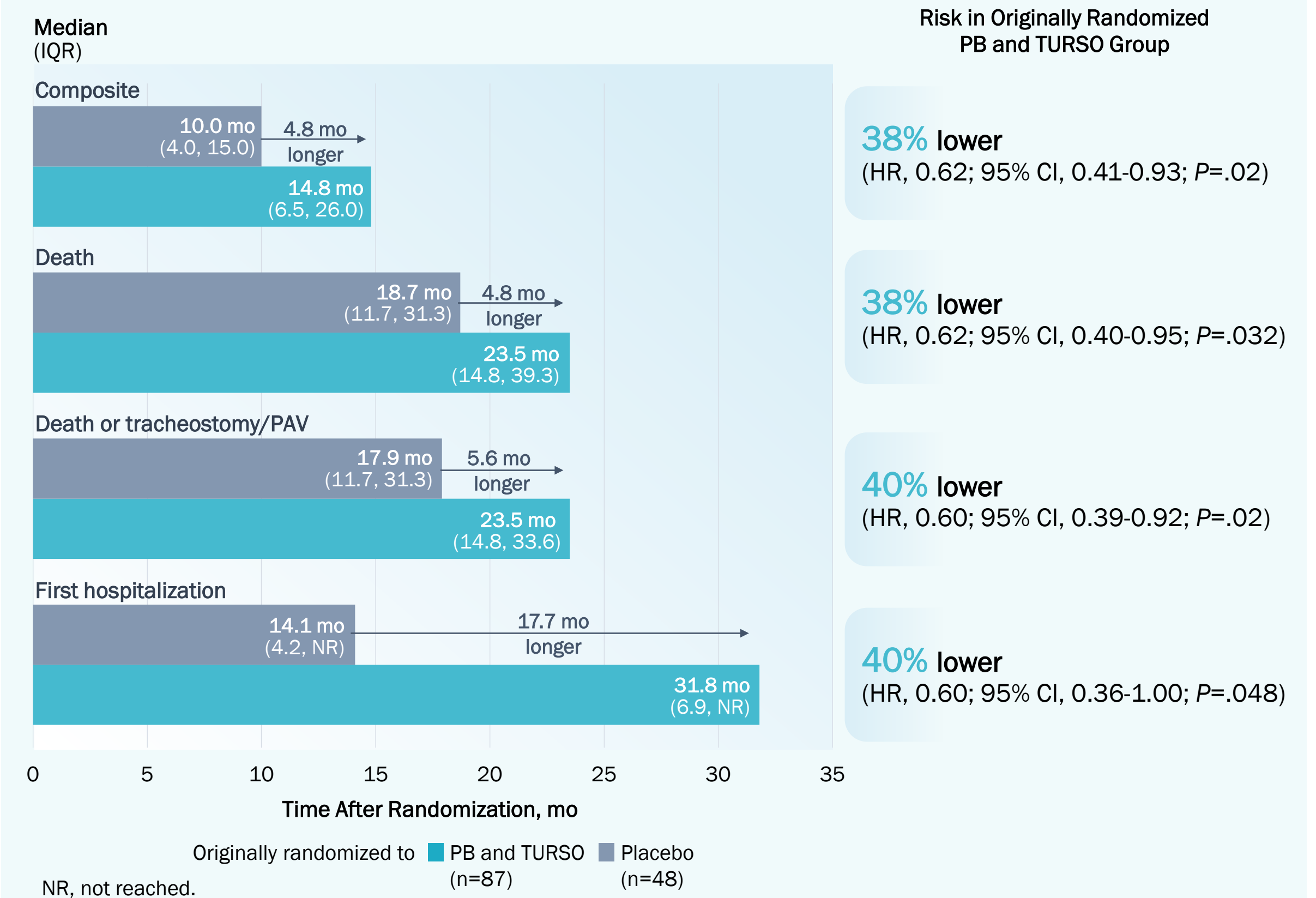
- The occurrence of all events was captured prospectively during participant monitoring within the randomized and OLE phases
- Median times to events and interquartile ranges (IQRs) were estimated from Kaplan-Meier curves
- Hazard ratios (HRs) were estimated using a Cox proportional hazards model with covariates of age at randomization, prebaseline ALSFRS-R slope, and baseline ALSFRS-R total score

CONCLUSIONS

- Long-term risk of death, tracheostomy/PAV, and first hospitalization was reduced among those originally randomized to PB and TURSO versus placebo
- Limitations include potential for missing data on tracheostomy/permanent assisted ventilation and first hospitalization due to loss to follow-up¹⁰
- The phase 3, global PHOENIX trial is currently underway; topline data are expected in mid-2024

RESULTS

Key Progression Events



- Median time to composite events was 4.8 months longer in the group receiving PB and TURSO, with a 38% lower risk
- 4.8-month longer median overall survival was observed with PB and TURSO compared with placebo
- Time to first hospitalization was significantly delayed with PB and TURSO compared with placebo as was time to tracheostomy/PAV

References

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