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: CO202

Janelle Schafer, PhD[1]; Suzanne Hendrix, PhD[2]; Sabrina Paganoni, MD, PhD[3,4]; on behalf of the CENTAUR Study Group

[1]Amylyx Pharmaceuticals, Inc., Cambridge, MA; [2]Pentara Corporation, Millcreek, UT; [3]Sean M. Healey and AMG Center for ALS & the Neurological Clinical Research Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA; [4]Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA

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 ALS[4-6]
- Therapies that slow disease progression have the potential to reduce short-term clinical burden in ALS[7]
- 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) phase[8]
  - 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 (ALSFRS-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 treatment[8]

[a]Also known as ursodoxicoltaurine.

OBJECTIVES

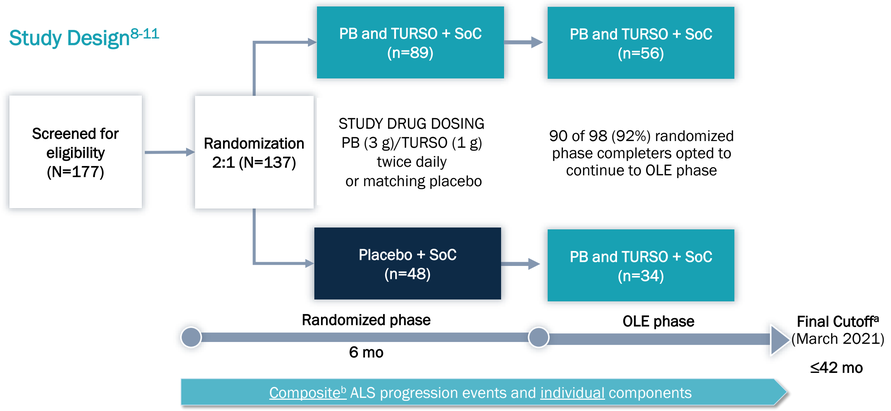
- Here, we report final analyses of ALS progression events in CENTAUR inclusive of the long-term, follow-up OLE phase, encompassing a postrandomization follow-up of ≤42 months
  - Analyses performed at an earlier timepoint have been previously published[8,9]
  - These final analyses are from the end 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) were[10]:
  - 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 OmniTrace[10]
  - 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 Design[8-11]



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.
[a]All 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.
[b]Composite includes death, tracheostomy/PAV, hospitalization.
[c]Oral 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 ALFSRS-R total score[10]

Statistical Analysis[10]

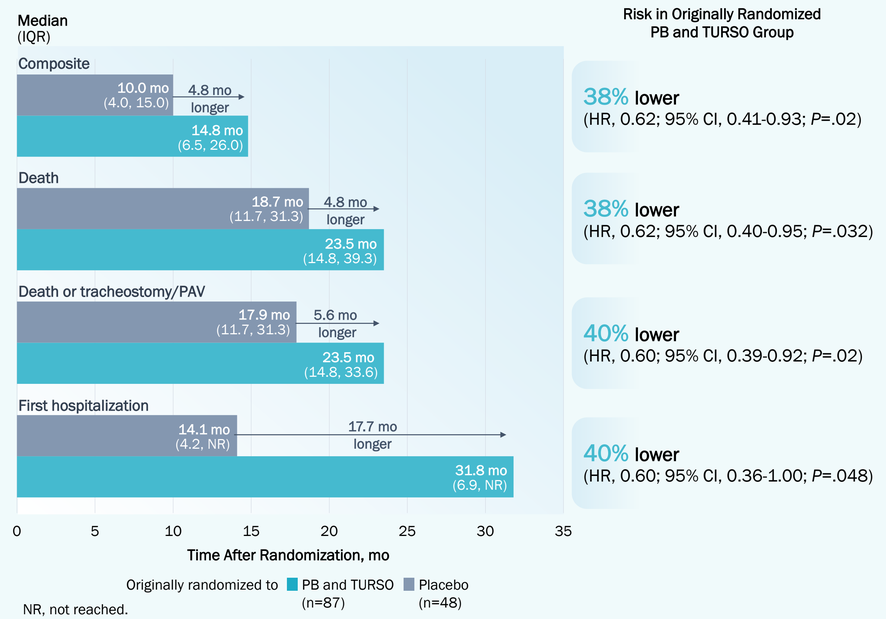
- The occurrence of all events was captured prospectively during participant monitoring within the randomized and OLE phases
- Median times to events and interquartile ranges (IQRs) were estimated from Kaplan-Meier curves
- Hazard ratios (HRs) were estimated using a Cox proportional hazards model with 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-up[10]
- 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

1. Niedermeyer S, et al. *Chest*. 2019;155(2):401-408. 2. van Es MA, et al. *Lancet*. 2017;390(10107):2084-2098. 3. Ang K, et al. *Proc Singapore Healthcare*. 2019;28(3):193-202. 4. Gladman M, Zinman L. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15(3):439-450. 5. Meng L, et al. *Amyotroph Lateral Scler Frontotemporal Degener*. 2018;19(1-2):134-142. 6. Larkindale J, et al. *Muscle Nerve*. 2014;49(3):431-438. 7. Gooch CL, et al. *Ann Neurol*. 2017;81(4):479-484. 8. Paganoni S, et al. *N Engl J Med*. 2020;383(10):919-903. 9. Paganoni S, et al. *Muscle Nerve*. 2022;66(2)136-141. 10. Paganoni S, et al. *J Neurol Neurosurg Psychiatry*. 2022;93(8):871-875. 11. Paganoni S, et al. *Muscle Nerve*. 2021;63(1):31-39. 12. Mitsubishi Tanabe Pharma America announces FDA approval of RADICAVA ORS® (edaravone) for the treatment of ALS. News release. May 13, 2022. Accessed April 18, 2023. https://www.prnewswire.com/news-releases/mitsubishi-tanabe-pharma-america-announces-fda-approval-of-radicava-ors-edaravone-for-the-treatment-of-als-301546937.html

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