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Short report

Effect of sodium phenylbutyrate/taurursodiol on tracheostomy/ventilation-free survival and hospitalisation in amyotrophic lateral sclerosis: long-term results from the CENTAUR trial

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ABSTRACT

Background Coformulated sodium phenylbutyrate/taurursodiol (PB/TURSO) was shown to prolong survival and slow functional decline in amyotrophic lateral sclerosis (ALS).

Objective Determine whether PB/TURSO prolonged tracheostomy/ventilation-free survival and/or reduced first hospitalisation in participants with ALS in the CENTAUR trial.

Methods Adults with El Escorial Definite ALS ≤ 18 months from symptom onset were randomised to PB/TURSO or placebo for 6 months. Those completing randomised treatment could enrol in an open-label extension (OLE) phase and receive PB/TURSO for ≤ 30 months. Times to the following individual or combined key events were compared in the originally randomised treatment groups over a period spanning trial start through July 2020 (longest postrandomisation follow-up, 35 months): death, tracheostomy, permanent assisted ventilation (PAV) and first hospitalisation.

Results Risk of any key event was 47% lower in those originally randomised to PB/TURSO (n=87) versus placebo (n=48, 71% of whom received delayed-start PB/TURSO in the OLE phase) (HR=0.53; 95% CI 0.35 to 0.81; p=0.003). Risks of death or tracheostomy/PAV (HR=0.51; 95% CI 0.32 to 0.84; p=0.007) and first hospitalisation (HR=0.56; 95% CI 0.34 to 0.95; p=0.03) were also decreased in those originally randomised to PB/TURSO.

Conclusions Early PB/TURSO prolonged tracheostomy/PAV-free survival and delayed first hospitalisation in ALS.

Trial registration number NCT03127514; NCT03488524.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disorder typically culminating in death from respiratory failure.^{1,2} Non-invasive ventilation (NIV) or, when NIV is not possible, tracheostomy and invasive ventilation may prolong survival and maintain or improve quality of life in people with ALS.^{1,3} From a societal standpoint, interventions such as assisted ventilation and hospitalisation are significant drivers of aggregate costs attributable to ALS in the USA each year.^{4,5} By slowing disease progression, therapies have the potential to reduce the short-term clinical burden associated with ALS.⁶

A fixed-dose sodium phenylbutyrate/taurursodiol (PB/TURSO) coformulation was designed to reduce neuronal death by simultaneously mitigating endoplasmic reticulum and mitochondrial dysfunction. PB/TURSO safety and efficacy were evaluated in the CENTAUR trial consisting of a randomised, double-blind, placebo-controlled phase (NCT03127514) and open-label extension (OLE) phase (NCT03488524). PB/TURSO administration was associated with a significantly slower rate of decline in ALS Functional Rating Scale-Revised (ALSFRS-R) total score compared with placebo over the 6-month randomised phase (primary outcome).⁷ In an intent-to-treat (ITT) analysis encompassing all 137 randomised participants in CENTAUR followed for up to 3 years after randomisation, long-term survival duration was significantly increased among those originally randomised to PB/TURSO versus placebo.⁸ Here, we report the results of prespecified analyses

evaluating the occurrence of key events in addition to death in CENTAUR, including tracheostomy, permanent assisted ventilation (PAV), and first hospitalisation.

METHODS

Detailed methodology for the trial is reported elsewhere,^{7,8} (see online supplemental file 2 for the full trial protocol and amendments). Briefly, adults with Definite ALS (revised El Escorial criteria)⁹ who were ≤ 18 months from symptom onset with a slow vital capacity $>60\%$ of predicted value were randomised 2:1 to receive PB/TURSO (3 g PB/1 g TURSO) or placebo by mouth or feeding tube for 6 months.⁷ Those completing randomised treatment were eligible to enrol in an OLE phase and receive PB/TURSO for up to 30 months. Continuation of a stable dose of riluzole and/or edaravone was permitted throughout the trial. Investigators, evaluators and participants were blinded to originally randomised treatment assignments.

Rates of the following key events were evaluated as a secondary efficacy outcome in CENTAUR: death (all-cause), tracheostomy (either for respiratory distress or airway clearance), PAV (defined as NIV >22 hours/day for >7 days), and hospitalisations specifically for ALS-related procedures (placement of a feeding tube, tracheostomy for management of secretions or respiratory support, or diaphragm pacing system) or due to a severe or serious adverse event, including those relating to progression or complications of ALS. The prespecified outcome was the composite of these key events.

Statistical analysis

The scope and methodology for all analyses are graphically summarised in online supplemental figure 1. The analyses encompassed occurrence of key events from the point of randomisation through a cut-off date of 20 July 2020 (longest postrandomisation follow-up, 35 months). The prespecified analysis population was the modified ITT (mITT) population, comprising all randomised participants who received at least one dose of originally assigned trial medication and had at least one postbaseline ALSFRS-R total score. All randomised 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.

Vital status was assessed for all randomised participants via prospective monitoring during the randomised and OLE phases of the trial or, in participants who discontinued, were lost to follow-up, or did not continue into the OLE phase, by a participant locating service (OmniTrace), via search of public records (online supplemental figure 1). The vital status of all but one randomised participant was successfully confirmed. Occurrence of other key events was primarily captured prospectively during participant monitoring within the trial (online supplemental figure 1). Analyses compared the time to each of the following individual or combined events in the originally randomised treatment groups: death; death, tracheostomy or PAV; first hospitalisation; and any key event. HRs were estimated using a Cox proportional hazards model with covariates of age at randomisation, prebaseline ALSFRS-R slope and baseline ALSFRS-R total score, as previously described.^{7,8} Median times to event(s) and associated IQRs were estimated from Kaplan-Meier curves. Tests were declared significant if the two-tailed p value was ≤ 0.05 .

RESULTS

Of 177 screened individuals, 137 were randomised in the double-blind phase (PB/TURSO, n=89; placebo, n=48); of 98

participants eligible for OLE phase enrolment, 90 (92%) elected to enrol (56 and 34 originally randomised to PB/TURSO and placebo, respectively). Two participants in the PB/TURSO group who died shortly after randomisation did not undergo a post-baseline ALSFRS-R assessment and were excluded from the prespecified mITT population. Detailed baseline characteristics of the mITT population are published elsewhere.⁷ Average participant age was 58 years, with mean durations of 13.5 and 6.0 months since ALS symptom onset and diagnosis, respectively. The majority (77%) of participants, including 71% originally randomised to PB/TURSO and 88% originally randomised to placebo, were receiving riluzole and/or edaravone at or prior to trial entry; among participants originally randomised to PB/TURSO and placebo, 68% and 77%, respectively, were receiving riluzole and 25% and 50%, respectively, were receiving edaravone. PB/TURSO exposure data for the originally randomised groups are summarised in online supplemental table 1.

Over the period spanning randomisation to the analysis cut-off date (longest postrandomisation follow-up, 35 months), the risk of any key event was 47% lower in those originally randomised to PB/TURSO versus placebo (HR=0.53; 95% CI 0.35 to 0.81; p=0.003); median (IQR) event-free durations were 14.8 (6.5–29.1) and 10.0 (4.0–15.0) months, respectively (figure 1A). Risk of death or tracheostomy/PAV was 49% lower among those originally randomised to PB/TURSO versus placebo (HR=0.51; 95% CI 0.32 to 0.84; p=0.007), with median (IQR) tracheostomy/PAV-free survival durations of 25.8 (14.8–33.6) months and 18.5 months (11.7 months—not reached (NR)), respectively (figure 1B). Risk of first hospitalisation was 44% lower in the group originally randomised to PB/TURSO (HR=0.56; 95% CI 0.34 to 0.95; p=0.03); median (IQR) hospitalisation-free duration was NR (6.9 months–NR) in those originally randomised to PB/TURSO versus 14.1 months (4.2 months–NR) in those originally randomised to placebo (figure 1C). Similar to the previously published ITT survival analysis, which included the two participants excluded from the mITT population who died shortly after randomisation,⁸ results of the death-only analysis in the prespecified mITT population showed a significantly lower risk of death with early-start PB/TURSO (online supplemental figure 2). Results for the remaining key event analyses were likewise similar between the mITT and ITT populations (online supplemental table 2).

DISCUSSION

In this long-term analysis of CENTAUR, the risk of key events including death, tracheostomy, PAV and first hospitalisation was significantly lower in those originally randomised to PB/TURSO compared with those originally randomised to placebo, most of whom went on to receive 6-month delayed-start PB/TURSO in the OLE phase. Median key event-free survival duration was 4.8 months longer in participants originally randomised to PB/TURSO versus placebo, and median tracheostomy/PAV-free survival duration was 7.3 months longer. As of the analysis cut-off, median time to first hospitalisation was not yet reached in the group originally randomised to PB/TURSO, compared with 14.1 months in the group originally randomised to placebo.

Among riluzole and edaravone, the two US Food and Drug Administration-approved therapies for ALS, only riluzole has shown a survival benefit in randomised clinical trials.^{10,11} However, the impact of riluzole on function in ALS is currently unclear.¹¹ PB/TURSO has shown a dual benefit on survival⁸ and function⁷ in ALS. The findings of prolonged tracheostomy/PAV-free survival and reduced hospitalisation incidence in the analyses described

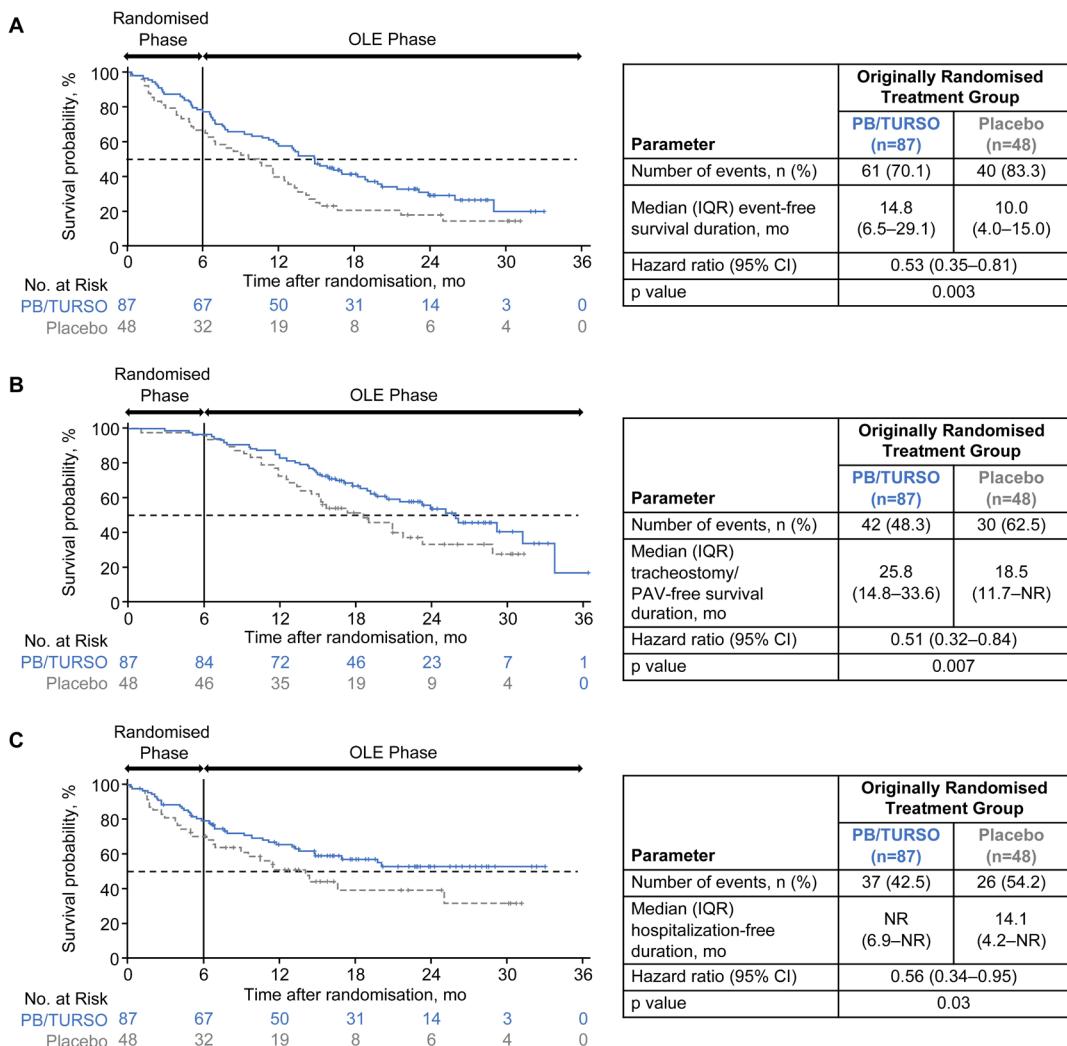


Figure 1 Kaplan-Meier analyses of time to key events. Time to (A) any key event (ie, death, tracheostomy, PAV or first hospitalisation), (B) death or tracheostomy/PAV and (C) first hospitalisation and corresponding median event-free duration estimates are shown for each originally randomised group in the modified intent-to-treat population (ie, all randomised participants who received at least one dose of originally assigned trial drug and had at least one postbaseline Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised assessment; N=135). HRs and p values were estimated using a Cox proportional hazards model. The numbers at risk exclude participants who experienced the analysed event(s) or were censored before that time point. OLE, open-label extension; PAV, permanent assisted ventilation (defined as non-invasive ventilation >22 hours/day for >7 days); PB/TURSO, sodium phenylbutyrate/taurusodiol.

herein support potential added benefits of PB/TURSO on reducing health burden in ALS.

Limitations

Because most participants who were originally randomised to placebo continued into the OLE phase and thus crossed over to PB/TURSO, the observed effect of early PB/TURSO may have been somewhat diluted in these analyses. In addition, while the use of a participant-locating firm allowed for definitive determination of vital status for all randomised participants but one, ascertainment of other key events was limited to the on-trial period, as these events are not captured in public records. As such, some postdropout tracheostomy, PAV, or hospitalisation events may not have been recorded in the subset of participants who discontinued from the trial, were lost to follow-up, or did not enrol in the OLE despite eligibility.

CONCLUSIONS

Early administration of PB/TURSO in the phase 2 CENTAUR trial prolonged tracheostomy/PAV-free survival and reduced

hospitalisation risk in ALS, thereby potentially reducing drivers of individual health burden. Adding to the previously reported overall survival and functional benefits attributable to PB/TURSO, these findings support a modifying effect of PB/TURSO on disease progression in ALS. The phase 3 PHOENIX trial (NCT05021536), which began enrolment in late 2021, will further evaluate PB/TURSO safety and efficacy outcomes, including the incidence of the key events analysed in CENTAUR, over 48 weeks in a more heterogeneous, international population of individuals with ALS.

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