Supplementary Online Content

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Table 1 PB/TURSO exposure duration data by originally randomised group*

Key Event Analysis	Parameter	PB/TURSO (n=87)	Placebo (n=48)
Any key event	Mean (SE), mo	7.5 (0.69)	1.6 (0.70)
Death and death or tracheostomy/PAV†	Mean (SE), mo	10.4 (0.87)	4.6 (0.87)
First hospitalisation	Mean (SE), mo	7.5 (0.69)	1.6 (0.70)

PAV, permanent assisted ventilation; PB/TURSO, sodium phenylbutyrate/taurursodiol; SE, standard error.
*PB/TURSO exposure in the group that started on placebo occurred entirely during the open-label phase.
†Differences between the mean PB/TURSO exposure durations for the death and death or tracheostomy/PAV analyses versus the any key event and first hospitalisation analyses are attributable to censoring of participants upon first hospitalisation.

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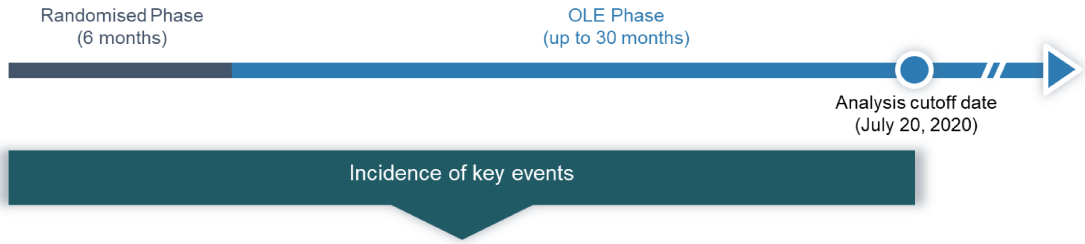
Table 2 ITT analyses of time to any key event, death or tracheostomy/PAV, and first hospitalisation

Key Event(s)	Parameter	Originally Randomised Treatment Group	
		PB/TURSO (n=89)	**Placebo (n=48)**
Any key event	Median (IQR) event-free survival duration, mo	14.8 (6.4–29.1)	10.0 (4.0–15.0)
	HR (95% CI)	0.55 (0.36–0.83)	
	P value	.005	
Death or tracheostomy/PAV	Median (IQR) event-free survival duration, mo	25.8 (14.6–33.6)	18.5 (11.7–NR)
	HR (95% CI)	0.54 (0.33–0.87)	
	P value	.012	
First hospitalisation	Median (IQR) event-free survival duration, mo	NR (6.9–NR)	14.1 (4.2–NR)
	HR (95% CI)	0.57 (0.34–0.96)	
	P value	.036	

HR, hazard ratio; IQR, interquartile range; ITT, intent-to-treat; NR, not reached; PAV, permanent assisted ventilation; PB/TURSO, sodium phenylbutyrate/taurursodiol.

Figure 1 Schematic summary of key events analyses in CENTAUR. The occurrence of key events including death, tracheostomy, PAV, and first hospitalisation was assessed from the point of randomisation through a cutoff date of July 20, 2020 (longest postrandomisation follow-up, 35 months). The analysis incorporated all randomised participants within the mITT population (ie, received at least one dose of originally assigned trial drug and had at least one postbaseline ALSFRS-R assessment; N=135). Death events were recorded prospectively during the course of the randomised phase and, for those who enrolled, the OLE phase of the trial; for randomised participants who discontinued from the trial, were lost to follow-up, or did not continue into the OLE phase, vital status and date of death (if applicable) were determined by OmniTrace, an investigative firm specializing in ascertaining vital status via search of public records. Censoring occurred at 1 month before the date of survival check for each participant, representing the maximum time for public records to capture any anteceding death events. Vital status could not be ascertained for one participant, a non-US resident for whom vital status could not be confirmed in US public records or by the clinical site; per the statistical analysis plan, this participant was censored at the date of last follow-up with the clinical site. Occurrence of other key events (ie, tracheostomy, PAV, or first hospitalisation) was primarily captured prospectively during the course of participant monitoring throughout the randomised and OLE phases. Participants without reported events were censored at the date of last follow-up. *Other events assessed in these analyses included tracheostomy, PAV (noninvasive ventilation >22 hours/day for >7 days), and first hospitalisation (specifically for ALS-related procedures [placement of a feeding tube, tracheostomy for management of secretions or for respiratory support, or diaphragm pacing system] or due to a severe or serious adverse event, including those relating to progression or complications of ALS). ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; mITT, modified intent-to-treat; OLE, open-label extension; PAV, permanent assisted ventilation.



Incidence of key events

Event	Population	Methods for Event Capture
Death	All randomised participants (mITT population)	• Prospective monitoring during trial (randomised and OLE phases) • OmniTrace search of public records in those who discontinued from study, were lost to follow-up, or did not continue into the OLE phase
Other events*		• Prospective monitoring during trial (randomized and OLE phases) • Censoring at date of last follow-up in those who discontinued from study, were lost to follow-up, or did not continue into the OLE phase

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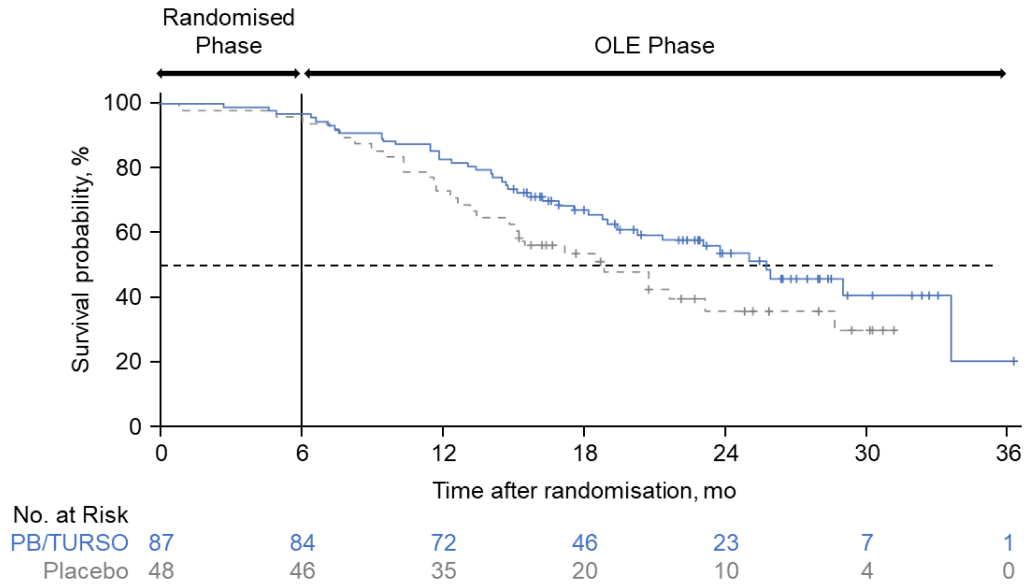
Figure 2 Kaplan-Meier analysis of time to all-cause death (mITT population). Time to death and median survival duration estimates were compared between the originally randomised treatment groups in the mITT population, the prespecified efficacy analysis population, at a cutoff date of July 20, 2020 (longest postrandomisation follow-up, 35 months). Hazard ratios and *P* values were estimated using a Cox proportional hazards model. Results of a similar analysis in the ITT population, consisting of all randomised participants, were previously reported.[1] The mITT analysis excluded two participants who were included in the ITT analysis who did not meet one of the prespecified criteria for inclusion in the mITT population (having at least one postbaseline ALSFRS-R assessment). Participants whose vital status could not be ascertained (n=1) were censored at the date of last follow-up. The numbers at risk exclude participants who died or were censored before that time point. ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; ITT, intent-to-treat; IQR, interquartile range; mITT, modified intent-to-treat; NR, not reached; OLE, open-label extension; PB/TURSO, sodium phenylbutyrate/taurursodiol.



Parameter	Originally Randomised Treatment Group	
	PB/TURSO (n=87)	Placebo (n=48)
Number of events, n (%)	41 (47.1)	29 (60.4)
Median (IQR) survival duration, mo	25.8 (14.8–33.6)	18.9 (11.7–NR)
Hazard ratio (95% CI)	0.54 (0.33–0.88)	
P value	.01	

Reference

1 Paganoni S, Hendrix S, Dickson SP, et al. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. *Muscle Nerve* 2021;63:31–9.