Determining Individual Substantial Response in Amyotrophic Lateral Sclerosis: Utilizing a New Method on CENTAUR Trial Results

Tracey Jason Lahar Mehta Yuehui Wu Jamie Timmons Sabrina Paganoni Merit Cudkowicz

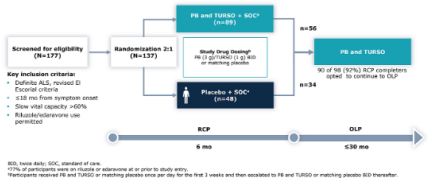
BACKGROUND

- In the CENTAUR study, an oral coformulation of sodium phenylbutyrate (PB) and ursodoxicoltaurine (TURSO) was associated with significantly slower functional decline as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) and significantly longer overall survival in participants with amyotrophic lateral sclerosis (ALS).[1,2] Similar adverse event rates were observed with PB and TURSO and placebo groups in the randomized placebo-controlled phase (RCP)[1]
- In addition to the CENTAUR primary analysis, which evaluated response as a mean group effect, evaluation of individual responses to active treatment versus placebo can also be informative. However, determining whether individual participants have a substantial response to a therapy is a challenge in ALS due to variable and rapid disease progression and the current lack of a universal definition for a "responder" in ALS clinical trials
- The prebaseline ALSFRS-R progression rate (ΔFS) is an independent predictor of survival and a reliable prognostic biomarker of ALS disease progression.[3] ΔFS frequently underestimates ALSFRS-R decline in clinical trials, providing a conservative individual benchmark for comparing rate of disease progression before and after initiation of treatment with study drug in a clinical trial[3-7]

METHODS

- Post hoc analysis of CENTAUR, a phase 2, multicenter study in adults with ALS encompassing a 6-month RCP and an open-label, long-term follow-up phase (OLP) (NCT03127514) (Fig 1)[1,2]
- **Primary objective:** Describe a new method of evaluating substantial individual response by comparing rate of disease progression before and after initiation of treatment with study drug and apply this method to data from the CENTAUR study RCP

Fig 1. CENTAUR study design[1,2,8]



METHODS (CONT)

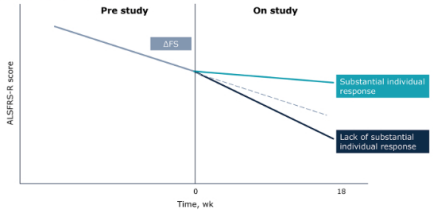
Post hoc substantial individual response analysis

- Performed comparing prebaseline ALSFRS-R progression rate (ΔFS) vs rate of change on study drug at week 18
- Rate of change on study drug was calculated as:

$$\text{Rate of change} = \frac{\text{ALSFRS-R (Wk 0 [study baseline])–ALSFRS-R (at Wk 18)}}{\text{Time}}$$

- **Substantial individual response in slowing ALS progression** defined as: participants whose actual rate of change in the ALSFRS-R at week 18 was less than their own prebaseline progression rate (ΔFS) (Fig 2)
- **Lack of substantial individual response in slowing ALS progression** defined as: participants whose actual rate of change in the ALSFRS-R at week 18 was greater than or equal to their own prebaseline progression rate (ΔFS) (Fig 2). Participants who died before Week 18 or withdrew before Week 12 were included in this group

Fig 2. Example: comparing rate of disease progression before study entry and at 18 weeks on study[3]



DISCLOSURES AND ACKNOWLEDGEMENTS (click here)

CONTACT INFORMATION

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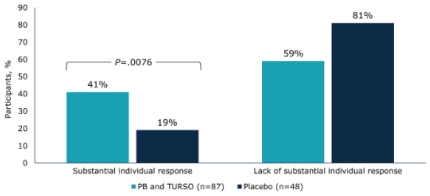
RESULTS

- Substantial individual response was observed in a greater proportion of participants receiving PB and TURSO (41%; 95% CI, 31%–52%) versus placebo (19%; 95% CI, 8%–30%) (Fig 3); odds ratio, 3.06; 95% CI, 1.32–7.09; *P*=.0076[8]

Fig 3. Individual response by treatment group[8]



CONCLUSIONS

- Comparing prebaseline ALSFRS-R progression rate versus rate of change on study drug provides a personalized metric to determine substantial individual response in ALS
- Application of this new method to CENTAUR data demonstrates a greater proportion of participants with a substantial individual response in the PB and TURSO group versus placebo
- Use of this method in ongoing and future studies may provide a conservative method to estimate treatment effect and enable greater personalization and analysis of individual response in ALS

REFERENCES

1. Paganoni S, et al. *N Engl J Med*. 2020;383(10):919-930.
2. Paganoni S, et al. *Muscle Nerve*. 2021;63:31-39.
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5. Labra J, et al. *J Neurol Neurosurg Psychiatry*. 2016;87:628-632.
6. Thakore NJ, et al. *Muscle Nerve*. 2018;57:937-945.
7. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. *Lancet Neurol*. 2017;16:505-512.
8. Amylyx data on file.

Determining Individual Substantial Response in Amyotrophic Lateral Sclerosis: Utilizing

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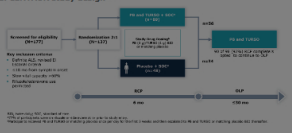

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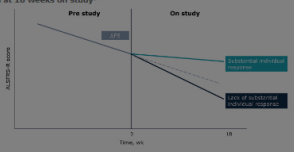

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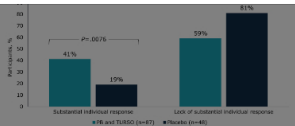

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