A Joint Model for Assessing Mortality-Adjusted Progression (MAP) in Amyotrophic Lateral Sclerosis: Application to Clinical Trials of Sodium Phenylbutyrate and Taurursodiol

Poster #CLT-30

Ruben van Eijk,[1,2] Feifan Zhang,[3] Yuehui Wu,[3] Ryan Miller,[3] Lahar Mehta,[3] Sabrina Paganoni,[4,5] Leonard van den Berg[2]

[1]Biostatistics and Research Support, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Department of Neurology, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Amylyx Pharmaceuticals, Inc., Cambridge, Massachusetts, USA; [4]Sean M. Healey and AMG Center for ALS & the Neurological Clinical Research Institute, Massachusetts General Hospital, Boston, Massachusetts, USA; [5]Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, Massachusetts, USA

BACKGROUND

- While understanding the impact of a therapy on both function and survival in amyotrophic lateral sclerosis (ALS) is important, these outcomes are often evaluated individually in clinical trials, using the ALS Functional Rating Scale–Revised (ALSFRS-R) for function and time to death/death-equivalent event for survival[1,2]
- Deaths occurring during the study may lead to informative missing data when evaluating ALSFRS-R as the primary end point, especially over longer trial durations[1-3]

OBJECTIVES

- Describe a joint model framework using a mortality adjusted mixed-effects model, Mortality Adjusted Progression (MAP), that includes survival data in the modelling and automatically accounts for deaths, while overcoming limitations of other methods **(Table 1)**
- Demonstrate the application of the MAP model and evaluate model performance using data from the 6-month randomized, placebo-controlled phase of the CENTAUR trial of sodium phenylbutyrate (PB) and ursodoxicoltaurine (also known as taurursodiol; TURSO) in ALS

TABLE 1. COMPARING THE HANDLING OF DEATHS DURING TREATMENT PERIOD ACROSS ANALYTICAL STRATEGIES[1-3]

Strategy	Advantages	Disadvantages
Linear mixed-effects model with no imputation for deaths	▪ Straightforward and simple method with direct interpretation for rate of decline	▪ Does not account for deaths; an important point in longer trials and for regulators
CAFS	▪ Accounts for deaths ▪ Well powered when treatment affects both function and survival	▪ Provides difficult-to-interpret treatment result
MAP	▪ Accounts for deaths ▪ Consistent and well powered across different scenarios ▪ Provides interpretable and clinically relevant result	▪ Computationally more complex ▪ Limited software support

CAFS, Combined Assessment of Function and Survival; MAP, Mortality-Adjusted Progression.

METHODS

- The prespecified primary efficacy analysis of CENTAUR evaluated the rate of ALSFRS-R total score progression using a shared-baseline, linear mixed-effects model in the modified intention-to-treat (mITT) population (PB&TURSO, n=87; placebo, n=48). The same model was performed on the intention-to-treat (ITT) population[4]
- The joint modeling framework incorporated all ALSFRS-R and survival data from the entire CENTAUR ITT population (PB&TURSO, n=89; placebo, n=48) in the MAP analysis[4]
  - Incorporated longitudinal ALSFRS-R data using a mixed-effects model and survival data using a parametric Weibull model[1]
  - A maximum likelihood estimation was then obtained by simultaneously maximizing the combined likelihood function of the ALSFRS-R score and the survival model

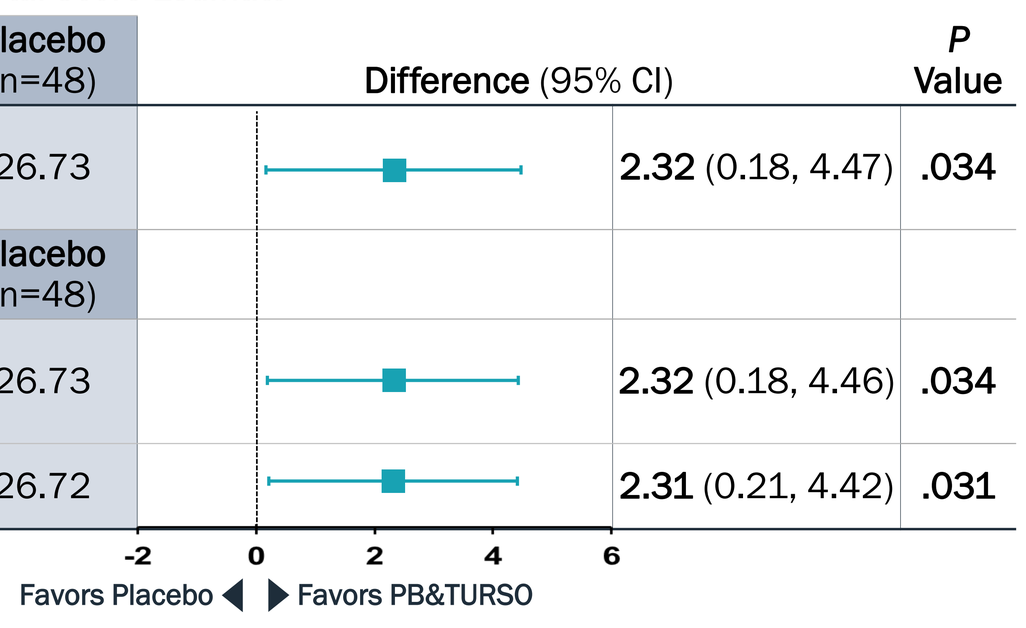
RESULTS

- In total, 7 deaths occurred during the 24-week randomized phase of CENTAUR (PB&TURSO, n=5 [5.6%]; placebo, n=2 [4.2%])[4]
- The results of the prespecified model in the mITT and ITT populations and the MAP model in the ITT population are summarized in **Figure 1**
- CENTAUR met its prespecified primary efficacy end point in the mITT population, and results were nearly identical in the ITT population using the prespecified linear mixed-effects model[4,5]
- Using the MAP model, minimal differences after adjustment for death resulted in nearly identical treatment effect sizes, with slightly increased precision

FIGURE 1. ANALYSES OF FUNCTIONAL PROGRESSION IN THE CENTAUR TRIAL

Week 24 LSM ALSFRS-R Total Score Estimate

Model	PB&TURSO (n=87)	Placebo (n=48)	Difference (95% CI)	*P* Value
Prespecified linear mixed-effects model (mITT[a])[4,5]	29.06	26.73	**2.32** (0.18, 4.47)	**.034**
	PB&TURSO (n=89)	**Placebo** (n=48)		
Prespecified linear mixed-effects model (ITT[b])	29.05	26.73	**2.32** (0.18, 4.46)	**.034**
Mortality adjusted progression (ITT[b])	29.04	26.72	**2.31** (0.21, 4.42)	**.031**



ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; ITT, intention-to-treat; LSM, least squares mean; mITT, modified intention-to-treat; MMRM, mixed model repeated measures; PB&TURSO, sodium phenylbutyrate and ursodoxicoltaurine.
[a]The mITT population was the prespecified efficacy analysis population in CENTAUR and comprised all randomized participants who received ≥1 dose of study drug and had ≥1 ALSFRS-R total score recorded after randomization.[4]
[b]The ITT population consisted of all randomized participants who received ≥1 dose of study drug, including 2 PB&TURSO-randomized participants who were excluded from the mITT population because they did not have a first postrandomization assessment.[4]

CONCLUSIONS

- MAP is a composite strategy to account for deaths, allowing adjustment for mortality while providing a result on functional benefit that is both easy to interpret and clinically relevant
- Post hoc application of this model to data from CENTAUR yielded similar results as the primary analysis, which was expected given that the incidence of deaths was overall low and similar between the treatment groups over the 24-week randomized phase
- Use of a MAP model is planned for the primary efficacy analysis in the ongoing phase 3 PHOENIX trial of PB&TURSO in ALS, with topline results anticipated in the second quarter of 2024

PB&TURSO is an investigational drug in the European Union, UK and Switzerland and not currently approved for use.

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Disclosures
- RvE, SP, and LvdB are members of the steering committee for the PHOENIX trial.
- FZ, YW, RM, and LM are full-time employees of and may have stock option ownership in Amylyx Pharmaceuticals, Inc.

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