

Rethinking Economic Evaluation in Amyotrophic Lateral Sclerosis Treatment: Embracing Alternative Model Conceptualizations

Sharma R¹, Davison N², Öhrman S³, Strican L³, Phatak H⁴

¹Maple Health Group LLC, NYC, US, ²Maple Health Group, LLC, Manchester, UK, ³Amylyx Pharmaceuticals EMEA B.V., Basel, CH, ⁴Amylyx Pharmaceuticals, Inc. Cambridge, US.

Presenting Author Contact Info: sara_ohrman@amylyx.com



Poster
#EE51

OBJECTIVES

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and universally fatal neurodegenerative disease affecting voluntary muscle control (i.e., speaking, swallowing, and breathing). The average life expectancy of people with ALS is 2-5 years from symptom onset. Riluzole, the only disease-modifying drug for the treatment of people living with ALS in the EU was approved over 25 years ago. In Europe, 6.22 per 100,000 people are impacted by ALS.¹ ALS progression is typically measured by the revised ALS Functional Rating Scale (ALSFRS-R). This clinical scale informs staging systems such as Milano-Torino system (MiToS), Fine ‘til 9 (FT9), and King’s. Thakore et al. (2020) developed a Markov model framework with health states based on FT9 stages to assess the cost-effectiveness of ALS treatments.³ This framework was the basis for health technology assessments (HTA) in Canada in 2021.⁴ In 2022, Amylyx conducted an advisory board with health economists from six European countries. The advisory board suggested that a partitioned survival model (PSM) may better represent the clinical benefits of treatments and the ALS disease course. The objective of this study considers how **best to conceptualize ALS treatment effects through a PSM** assessing the cost-effectiveness of the sodium phenylbutyrate (PB) and ursodoxicoltaurine (also known as taurursodiol; TURSO) versus best supportive care (BSC), both including approved ALS medications if appropriate.

METHODS

A targeted literature review (TLR) was conducted to assess data availability for a cost-effectiveness analysis, and an early PSM was developed. The model partitioned overall survival using hospitalization-free survival (a composite endpoint of time to first hospitalization or death). Patients in the model therefore existed in one of three health states: **pre-hospitalization, post-hospitalization, or death**. Overall survival and hospitalization free survival Kaplan Meier (KM) data were sourced from the intention-to-treat (ITT) population of the PB and TURSO Phase 2 clinical trial (CENTAUR).⁵ **Crossover-unadjusted and crossover-adjusted** analyses were considered. The crossover-adjusted survival was informed by a rank-preserving structural failure time model (RPSFTM) analysis, using the most conservative adjustment method (re-censoring acceleration factor only).⁶ The proportional hazards assumption was assessed via log cumulative hazard plots and Schoenfeld residual plots. Survival extrapolations were explored jointly (stratified by treatment group) and separately for exponential, gamma, generalized gamma, Gompertz, log-logistic, log-normal, and Weibull distributions. The selected distributions (see Figure 1) were based on goodness-of-fit statistics and best visual fit. The analysis was completed for **two key populations**: the overall ITT population and an edaravone-free subpopulation which excluded patients who began edaravone treatment post-baseline. The edaravone-free subpopulation aligns more closely with European clinical practices as edaravone is not approved by the European Medicines Agency (EMA).

RESULTS

In previous HTAs of ALS treatments, Markov transition probabilities were based on the literature, with treatment effects applied using relative risks. A partitioned survival model allows inclusion of **crossover-adjusted survival from trial data in a technically robust manner**. Figure 2 illustrates the impact of including the crossover-adjusted approach in the analysis. **The majority of incremental LYs are gained in the pre-hospitalization state** when comparing PB and TURSO to BSC (see Table 1). The proportion of patients in the pre- and post-hospitalization health states can be associated with costs and utilities to calculate total or incremental costs and QALYs, and therefore an **incremental cost-effectiveness ratio**.

Figure 2. TOTAL AND INCREMENTAL LIFE YEAR RESULTS FOR ITT VS. CROSSOVER-ADJUSTED ANALYSES FOR THE OVERALL POPULATION AND EDARAVONE-FREE POPULATION

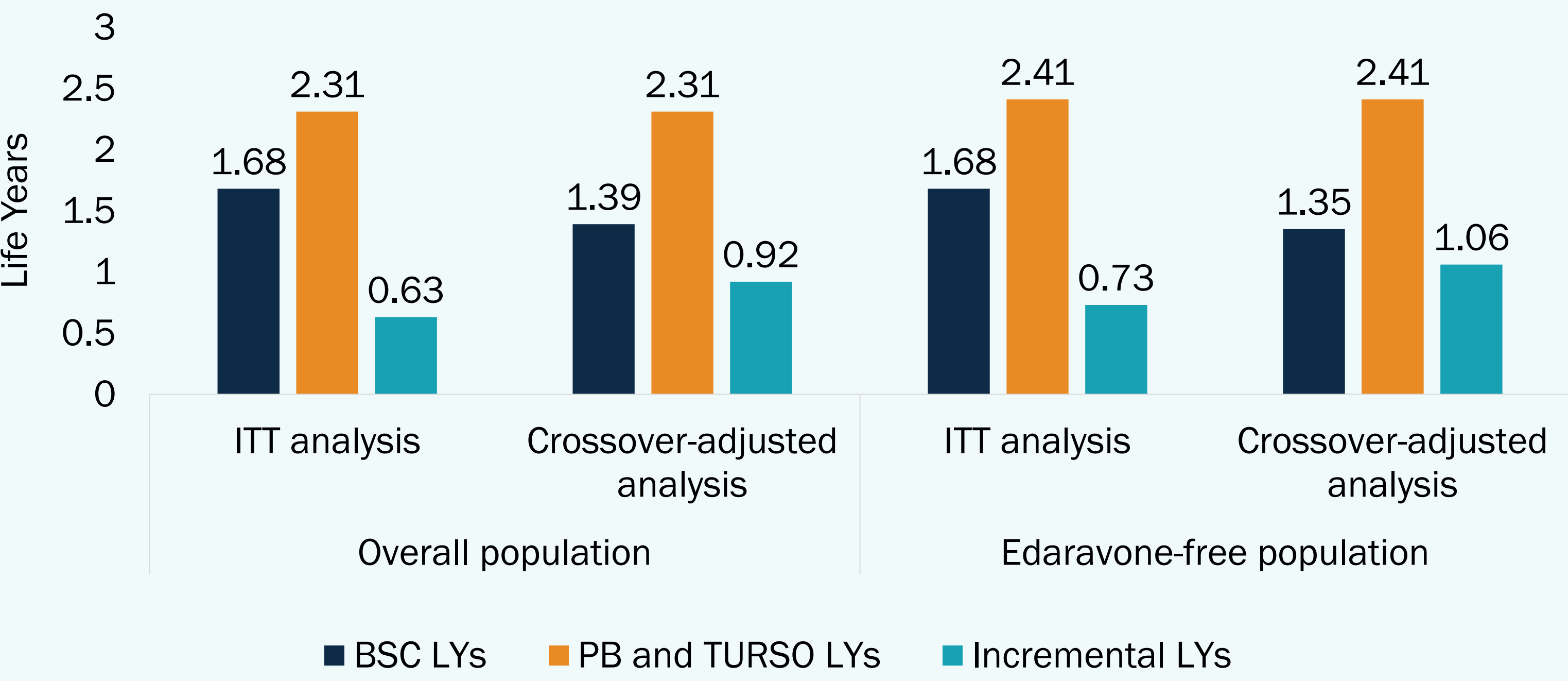


Figure 1. OVERALL POPULATION CROSSOVER-ADJUSTED ANALYSIS OVERALL SURVIVAL AND HOSPITALIZATION-FREE SURVIVAL KM CURVES AND SURVIVAL EXTRAPOLATIONS

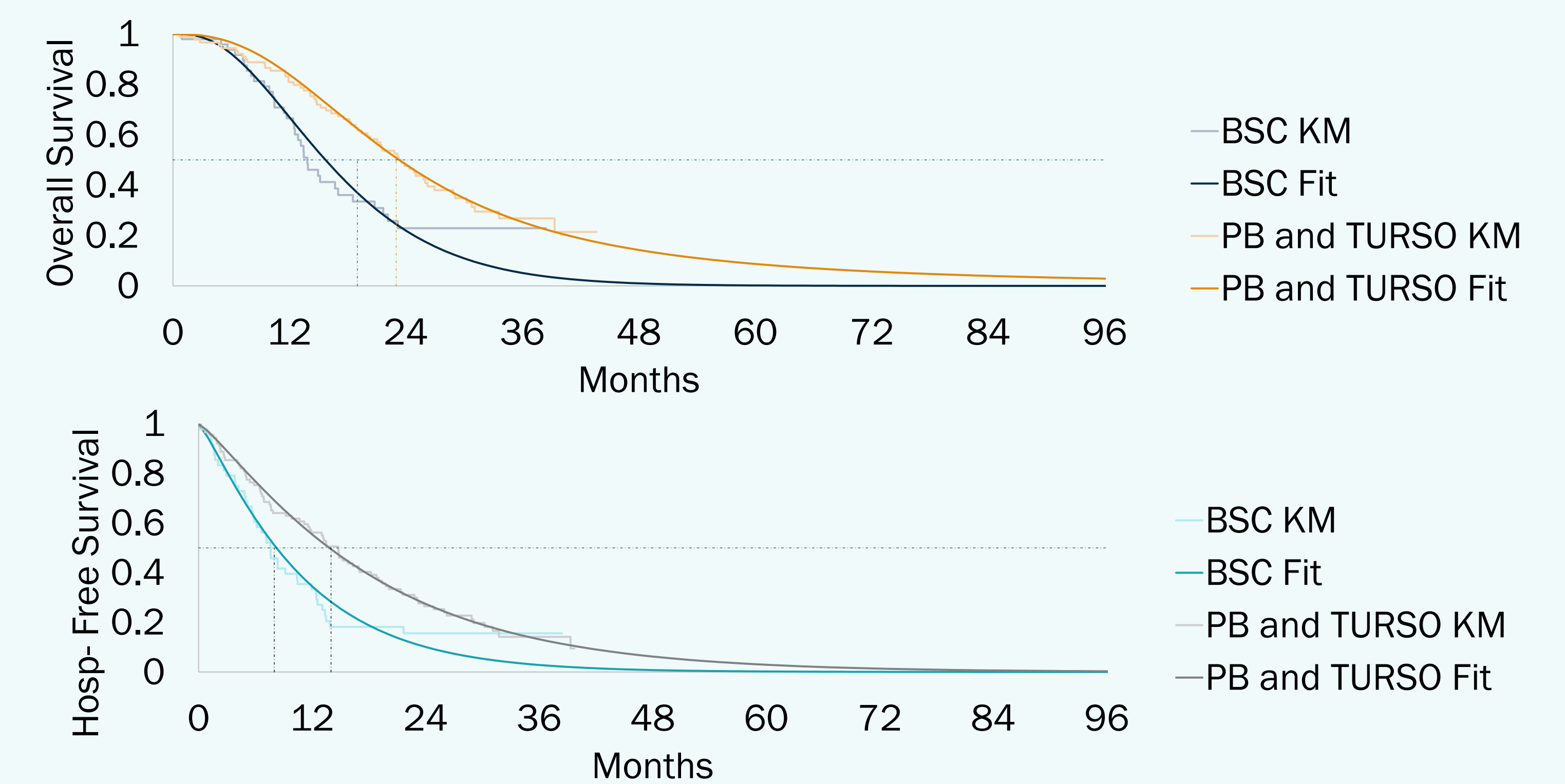


Table 1. COMPARING PRE-HOSPITALIZATION AND POST-HOSPITALIZATION LIFE YEARS IN THE OVERALL POPULATION CROSSOVER-ADJUSTED ANALYSIS

	Pre-Hospitalization		Post-Hospitalization	
	LYs	% Absolute Increment	LYs	% Absolute Increment
BSC	0.86	-	0.53	
PB and TURSO	1.45	64.10%	0.86	35.90%

References
¹Brown CA, Lally C, Kupelian V, Flander WD. Estimated Prevalence and Incidence of Amyotrophic Lateral Sclerosis and SOD1 and C9orf72 Genetic Variants. *Neuroepidemiology* 2021; 55(5): 342-353.
²Arthur KC, Calvo A, Price TR, Geiger JT, Chio A, Traynor BJ. Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. *Nat Commun* 2016; 7: 12408.
³Thakore NJ, Pioro EP, Udeh BL, Lapin BR, Katzan IL. A Cost-Effectiveness Framework for Amyotrophic Lateral Sclerosis, Applied to Riluzole. *Value Health* 2020; 23(12): 1543-51.
⁴Canadian Agency for Drugs and Technologies in Health. CADTH Reimbursement Review: Sodium phenylbutyrate-ursodoxicoltaurine. *Canadian Journal of Health Technologies* 2022;2 (10)
⁵Amylyx Data on File. CENTAUR Study (Data cut-off: 1st March 2021) overall survival and time to event analyses. 2023.
⁶Paganoni S, Watkins C, Cawson M, Hendrix S, Dickson SP, Knowlton N, Timmons J, Manuel M, Cudkowicz M. Survival analyses from the CENTAUR trial in amyotrophic lateral sclerosis: Evaluating the impact of treatment crossover on outcomes. *Muscle Nerve* 2022 Aug;66(2):136-141.
⁷European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS). 2015; EMA/531686/2015, Corr.1.
⁸Moore A, Young CA, Hughes DA. Health Utilities and Costs for Motor Neurone Disease. *Value Health* 2019; 22(11): 1257-65.
Abbreviations
ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale; BSC, best supportive care; EMA, European Medicines Agency; FT9, Fine ‘til 9; Hosp-free, hospitalization free survival; HTA, health technology assessments; ITT, intention to treat; KM, Kaplan Meier; LY, life years; MiToS, Milano-Torino Staging System; OS, overall survival; PB and TURSO; phenylbutyrate and ursodoxicoltaurine also known as taurursodiol; PSM, partitioned survival model; QALYs, quality adjusted life years.
Disclosures
SÖ and LS are full-time employees of Amylyx Pharmaceuticals EMEA B.V. (Swiss Branch) and may have stock option ownership in Amylyx Pharmaceuticals, Inc. HP is a full-time employee of and may have stock option ownership in Amylyx Pharmaceuticals, Inc.
Acknowledgements
This study is sponsored by Amylyx Pharmaceuticals, EMEA B.V.

CONCLUSIONS

Recommended study objectives for clinical studies in ALS are increased survival and delay of disease progression.⁷ A PSM can use direct survival data from a clinical trial through patient level data and Kaplan-Meier information. Hospitalization is known to be an important inflection point in the disease pathway. A potential limitation to the PSM approach with a single partition is that information on subsequent worsening is lost. However, the TLR suggested little differentiation in utility and healthcare resource use between later disease stages (i.e., MiToS stages 2 through 4), which could be pooled for post-progression inputs.⁸ A PSM seems to be a viable approach to capture the value of novel ALS interventions.

PB&TURSO is an investigational drug in the European Union, UK and Switzerland and not currently approved for use
Edaravone is an investigational drug in the European Union and UK and not currently approved for use
© 2023 Amylyx Pharmaceuticals EMEA B.V.