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

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Poster
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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

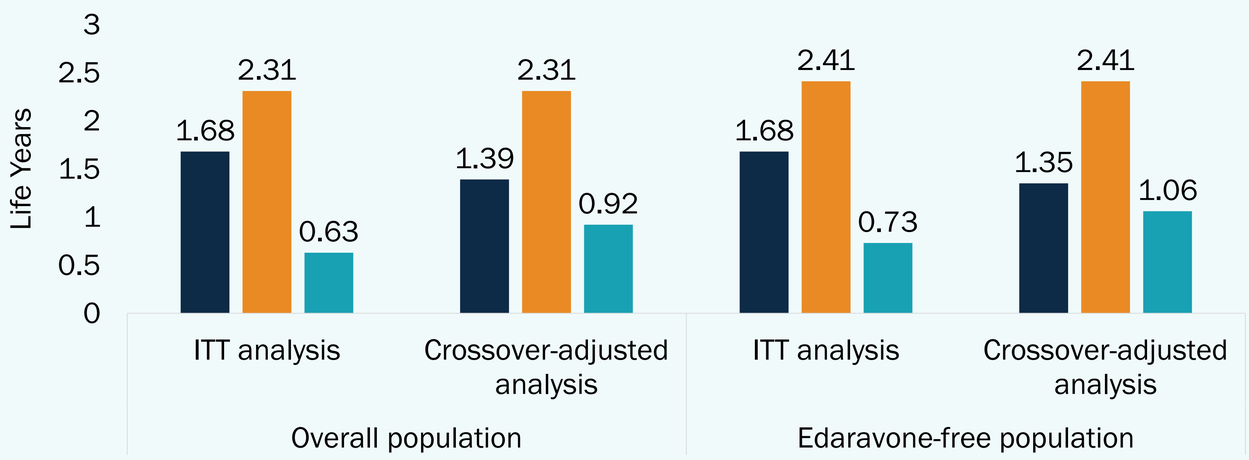

Figure 1. OVERALL POPULATION CROSSOVER-ADJUSTED ANALYSIS OVERALL SURVIVAL AND HOSPITALIZATION-FREE SURVIVAL KM CURVES AND SURVIVAL EXTRAPOLATIONS

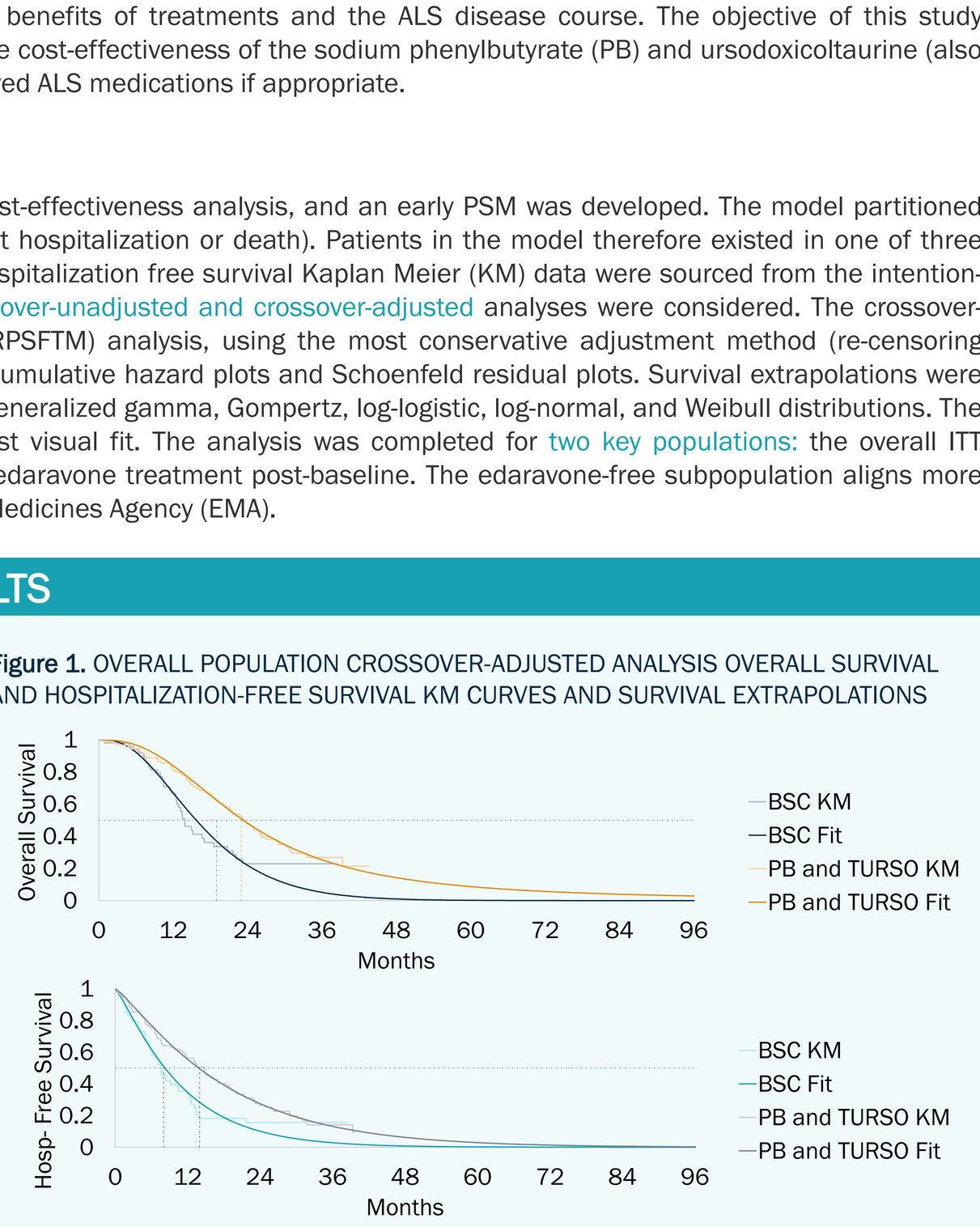

Table 1. COMPARING PRE-HOSPITALIZATION AND POST-HOSPITALIZATION LIFE YEARS IN THE OVERALL POPULATION CROSSOVER-ADJUSTED ANALYSIS

	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%

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.

References

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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.

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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

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