Estimating the Effect of a Discontinued Amyotrophic Lateral Sclerosis Treatment on Time to Death Using Sequential Target Trial Emulation

Queeny Ip, Yuqin Wei, Ting-Ying Huang, Ahmed Noman, Kenneth Taylor — Komodo Health, New York, NY, and San Francisco, CA

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Introduction

- Amyotrophic lateral sclerosis (ALS) is a rare, fatal neurodegenerative disease that affects the ability to move, speak, swallow, and eventually breathe, and afflicts approximately 30,000 Americans[1]
- Only 10% of ALS cases are hereditary (the cause of remaining cases is unknown) and symptom onset is most common between the ages of 60 and the mid-80s, with an average time-to-death of 2 to 5 years[2]
- All approved treatments are to improve functional abilities and slow disease progression[2]
- The combination of sodium phenylbutyrate and taurursodiol (SP-T) was approved by FDA for ALS treatment on September 22, 2022, but was later voluntarily withdrawn from the US market on April 4, 2024, after failing to find a significant difference in functional score (ALSFRS-R) compared to placebo in phase 3 trial[3,4]
- An open-label extension phase of the trial is ongoing to collect survival data (results in 2026)[3,4]
- We aim to conduct a retrospective claims database study to compare time-to-death between ALS patients who initiated SP-T and those who did not initiate SP-T[5]

Objective

- To conduct a sequential target trial emulation study to estimate the effect of SP-T initiation on time-to-death

Methods

Data Source

- This retrospective cohort study used genomics data from NeoGenomics to validate a claims-based identification algorithm[1-3] in the Komodo Research Dataset (KRD), a database of administrative data and claims capturing routinely collected health services utilization records and expenditures for over 330 million de-identified unique individuals in the U.S.

Komodo Research Dataset (KRD): *Composed of administrative data and claims, KRD captures routinely collected health services utilization records for over 330 million de-identified unique individuals in the United States. Native to HIPAA-compliant, privacy-preserving tokens, KRD offers extended patient-level observations of medical encounters and outpatient pharmacy dispensings via linkage across health and pharmacy insurance plans. Data availability is as early as 2016. Specialty datasets such as genomics, laboratory test results, and electronic medical records are readily accessible via additional linkage. KRD is the optimized schema of the underlying Healthcare Map® from Komodo Health for real-world evidence generation.*

Komodo Mortality Insights (KMI): *Death information derived from a combination of Social Security Administration's Death Master File, state mortality registries, curated public death notices, and other data provider proprietary data. Pre-certified for dataset linkage via privacy-preserving tokens.*

Komodo Race & Ethnicity (KRE): *Self-reported or health care provider/system-assigned race and ethnicity information for over 200 million unique individuals obtained from assorted categories of data sources including electronic health records, patient intake forms, payer enrollment files, and statistically reliable consumer reporting agencies in the United States.*

Study Design

- We implemented the target trial framework to emulate a sequence of hypothetical randomized trials comparing SP-T initiators vs non-initiators (standard care [riluzole or edaravone]) in each calendar month from October 2022 to March 2024 to estimate the observational analog of the intention-to-treat effect
- Initiators in a given emulation were considered ineligible in subsequent emulation months
- Optimal full matching targeting the average treatment effect to account for confounding with 44 pre-index demographic and clinical characteristics as covariates in our propensity score model, with exact matching on emulation month
- Patients were followed from index date to either death or September 30, 2024 (whichever occurred first)
- Data were pooled across all emulations to estimate survival time (via Kaplan-Meier estimator) and the effect on time-to-death (via Cox proportional hazards model), estimating 95% confidence intervals via bootstrapping since unique individuals could contribute to multiple emulations in the sequence

Inclusion/Exclusion Criteria (see Figure 1)

- Patients were included if they were treated with SP-T or standard of care treatments for ALS between October 1, 2022 and March 31, 2024
- Each treatment dispensation date within the emulation start month was assessed for eligibility
  - ≥2 claims with ALS diagnosis code (ICD-10-CM G12.21) OR ≥1 claim for standard of care treatment within 2 years (730 days) before the dispensation date
  - Patients having claims with ALS diagnosis codes OR standard of care treatment prior to the 2-year window before the dispensation date were excluded
  - Patients with intermittent medical and drug enrollment during the 6 months (183 days; allowable gaps ≤45 days) before the treatment dispensation date were excluded
  - Patients with evidence of ≥14 days of supply for standard of care received in the 6 months (183 days) before the dispensation date
  - Patients ≥18 years of age on the dispensation date
  - Patients without any prior SP-T exposure on the dispensation date

SP-T initiator cohort

- Patients with an eligible dispensation where they initiated SP-T in each emulation calendar month were assigned to the SP-T initiator cohort with their index date assigned to the date of SP-T initiation for that specific trial emulation

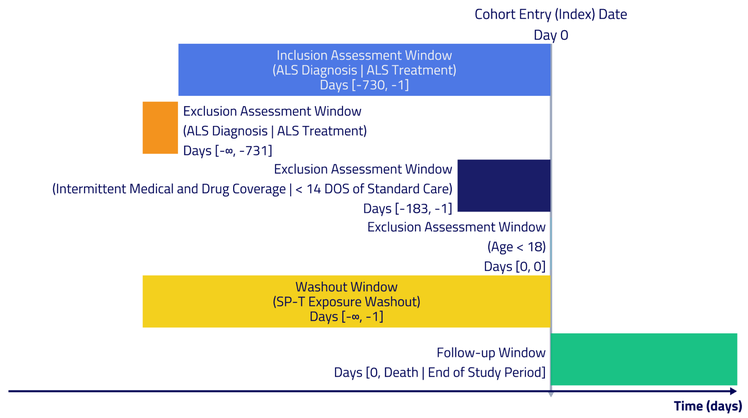
Non-SP-T initiator (control) cohort

- Patients with eligible treatment dispensations in a given emulation calendar month, but without any of them being SP-T were assigned to the control cohort with their index date assigned to a random dispensation date out of all eligible dispensation dates during that emulation calendar month

Key Study Variables

- Demographics and clinical characteristics
- Death date — for HIPAA compliance reasons, death dates are provided truncated to the year and month of death (YYYY-MM-01)

Figure 1. Study design diagram



Results

- Analyzed sample: 3,117 unique patients; 709/10,692 (SP-T initiators/non-initiators) non-unique patients
- Post-matching balance achieved with median age of 62/63 years, 40%/44% women, 65%/60% white, and 61%/54% with commercial insurance
- After incorporating matching weights, 2,570 non-unique deaths were observed (119/2,451 [initiator/non-initiator]) over 788 days (see **Figure 2**)
- Unadjusted and adjusted survival curves are presented in **Figure 3** and **Figure 4**, respectively
- The estimated unadjusted and adjusted effect of SP-T initiation on time-to-death is presented in **Table 1**

Figure 2. Unique and non-unique deaths by calendar time

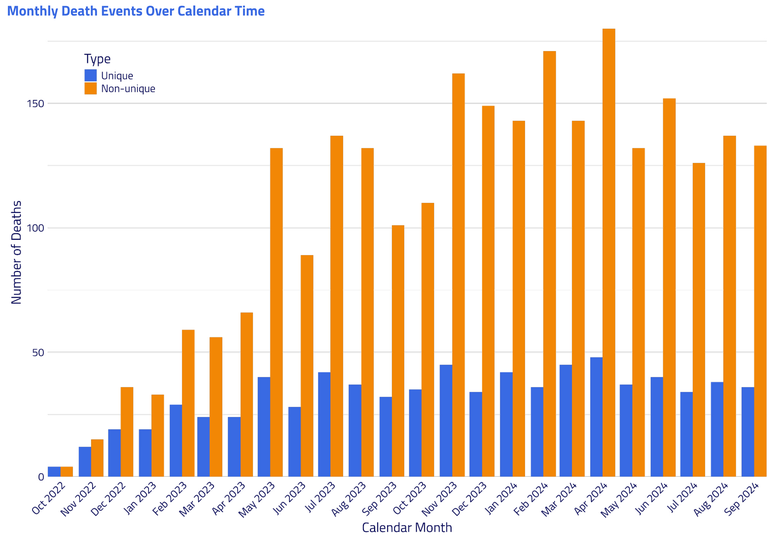


Figure 3. Unadjusted survival probability over time

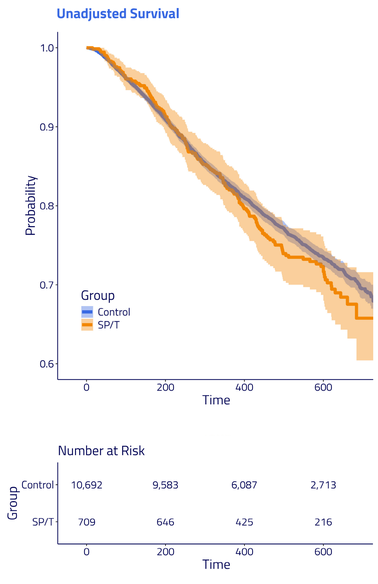


Figure 4. Adjusted survival probability over time (weighted using weights from optimal full matching)

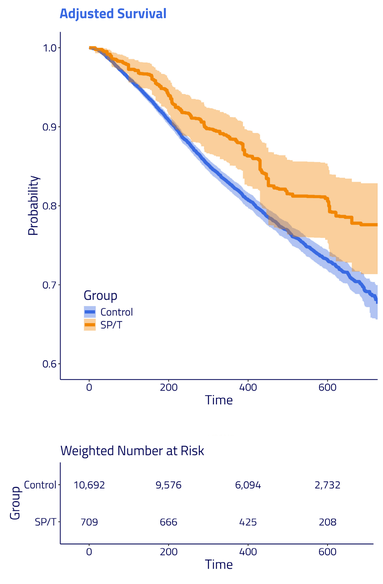


Table 1. Cox proportional hazards model results

Characteristic	Event N	Hazard Ratio	95% Confidence Interval	*P*-value
Unadjusted				
Control	2,418	—	—	
SP-T	180	1.09	0.94 to 1.27	0.24
Adjusted[a]				
Control	2,451	—	—	
SP-T	119	0.70	0.50 to 0.83	0.001

[a] *Weighted using weights from optimal full matching*

Conclusion

- Utilizing a sequential target trial emulation in estimating the effect of SP-T initiation on time-to-death, our results suggest a lower risk for death for ALS patients who initiated SP-T compared with non-initiators

References

[1] CDC. "About the National ALS Registry." National Amyotrophic Lateral Sclerosis (ALS) Registry, 14 Nov. 2024, https://www.cdc.gov/als/abouttheregistrymain/index.html

[2] "How Is ALS Diagnosed and Treated? | ALS Program at HSS." Hospital for Special Surgery, https://www.hss.edu/condition-list_amyotrophic-lateral-sclerosis.asp. Accessed 7 Apr. 2025

[3] Amylyx Pharmaceuticals Announces Topline Results From Global Phase 3 PHOENIX Trial of AMX0035 in ALS | Amylyx. 8 Mar. 2024, https://www.amylyx.com/news/amylyx-pharmaceuticals-announces-topline-results-from-global-phase-3-phoenix-trial-of-amx0035-in-als

[4] Shapiro, Lindsey. AAN 2024: ALS Trial Investigator Shares Details of Relyvrio Failure. 16 Apr. 2024, https://alsnewstoday.com/news/aan-2024-als-trial-investigator-shares-details-relyvrio-failure/

[5] Amylyx Pharmaceuticals Inc. A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial to Evaluate the Safety and Efficacy of AMX0035 Versus Placebo for 48-Week Treatment of Adult Patients With Amyotrophic Lateral Sclerosis (ALS). Clinical trial registration, NCT05021536, clinicaltrials.gov, 9 Aug. 2024. clinicaltrials.gov, https://clinicaltrials.gov/study/NCT05021536

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