Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Paganoni S, Macklin EA, Hendrix S, et al. Trial of sodium phenylbutyrate–taurursodiol for amyotrophic lateral sclerosis. N Engl J Med 2020;383:919-30. DOI: 10.1056/NEJMoa1916945

Table of Contents

1. CENTAUR Clinical Trial Sites and Site Investigators

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Emory University	Christina N. Fournier, M.D.
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University of Kentucky	Edward J. Kasarskis, M.D., Ph.D.
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Ochsner Health System	Kristin M. Johnson, D.O.
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Johns Hopkins University	Jeffrey D. Rothstein, M.D., Ph.D.
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The Ohio State University	Adam Quick, M.D.
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2. Supplementary Introduction

Section 2.1. Proposed Mechanisms of Action of Sodium Phenylbutyrate and Taurursodiol in ALS

Endoplasmic reticulum stress or dysfunction associated with protein misfolding and aggregation has been implicated in the pathogenesis of ALS,[1] as has disruption of mitochondrial function and structure.[2] Sodium phenylbutyrate is a histone deacetylase inhibitor that has been shown to upregulate heat shock proteins and act as a small molecular chaperone, thereby ameliorating toxicity from endoplasmic reticulum stress.[3,4] Taurursodiol recovers mitochondrial bioenergetic deficits through several mechanisms, including by preventing translocation of the Bax protein into the mitochondrial membrane, thus reducing mitochondrial permeability and increasing the apoptotic threshold of the cell.[5]

3. Supplementary Methods

Section 3.1. Randomization Procedures

The randomization schedule was computer generated by an unblinded statistician using SAS (version 9.4, SAS Institute, Cary, NC). Eligible participants were randomized in a 2:1 ratio to receive either sodium phenylbutyrate–taurursodiol or matching placebo using a permuted block structure with blocks of three and six and no additional stratification. Trial drug was dispensed in kits with random four-digit identification numbers from a central pharmacy. Kits were sent in sequence to sites as each new participant was enrolled. Participants were assigned to treatment based on the kit they received. Due to an error in initial kit distribution at the central pharmacy depot, the first 17 participants received active drug, while the next nine participants received placebo. A sensitivity analysis was conducted from which participants who were affected by this shipping event were excluded; this analysis yielded similar results to the prespecified primary analysis (between-group mean ALSFRS-R slope difference of 0.46 (P=0.04) vs. 0.42 (P=0.03) in the primary analysis). Treatment allocations after these first 26 participants followed the original randomization schedule.

Section 3.2. Trial Drug Preparation and Administration

The active drug has a bitter taste, and the placebo formulation was designed to have a matched bitter taste, appearance, and dissolution profile to prevent unblinding concerns.

The following instructions for trial drug preparation and administration were verbally provided to participants at the baseline visit by a health care staff member.

- Trial drug should be taken (or administered) prior to a meal.

- Rip open the sachet of trial drug and pour the contents into a cup or other container.
- Add approximately 8 ounces of room-temperature water and stir vigorously. (Trial drug may require significant stirring or gentle crushing to dissolve.)
- Consume or administer via gastrostomy or nasogastric tube completely and within 1 hour of combining the contents of the sachet with water. Use of Thick-It® is permitted for oral administration.
- Do not take or administer antacids containing aluminum hydroxide or smectite (aluminum oxide) within 2 hours of administration of the trial drug as they inhibit absorption of taurursodiol.
- Resume normal eating and drinking after taking the trial drug.

Participants were informed that the trial drug (active and placebo) has a strong bitter taste and were advised of strategies for making the drug more palatable if taking orally, including:

- Using Listerine Pocket Packs® (strips) or Listerine PocketMist® (spray) liberally, to coat the mouth, immediately before and/or after taking the drug
- Consuming a snack or a meal after taking the drug
- Following the drug immediately with milk
- Avoiding intake of fruit juice at the same time as the trial drug, as this may make flavor worse

Section 3.3. ATLIS Methodology

The ATLIS device measures isometric strength in six upper- and six lower-limb muscle groups with a high degree of reproducibility using a fixed, wireless dynamometer with standard

positions, rather than relying on examiner strength.[6] Two attempts of each maneuver were performed during every assessment, adding a third attempt if the first two differed by more than 15%. Raw values were standardized to percentage of predicted normal strength based on sex, age, weight, and height[7] and expressed using mean scores for upper-limb, lower-limb, and total ATLIS percentage of predicted normal values. ATLIS scores for each participant and visit were then submitted to the following steps in order to be used for analysis:

1. Predicted values were determined for each of the 12 muscle groups using the participant's baseline information (sex, age, weight, and height) and the coefficient and intercept estimates provided in the table that follows.

Coefficients and Intercepts for ATLIS Standardization[7,*]

Sex	Maneuver	Age (years) Coefficient	Weight (lb) Coefficient	Height (in) Coefficient	Intercept
Female	Left grip	−0.15	0.16	1.18	−28.91
	Right grip	−0.21	0.18	1.05	−14.01
	Left elbow flexion	−0.04	0.14	0.44	−6.03
	Right elbow flexion	−0.07	0.13	0.49	−6.95
	Left elbow extension	−0.09	0.1	0.09	12.14
	Right elbow extension	−0.09	0.08	0.13	13.37
	Left knee extension	−0.231	0.231	0.352	21.263
	Right knee extension	−0.231	0.165	0.319	32.604
	Left knee flexion	−0.14	0.08	0.62	−12.64
	Right knee flexion	−0.19	0.09	0.65	−14.23
	Left ankle dorsiflexion	−0.13	0.1	0.06	23.63
	Right ankle dorsiflexion	−0.08	0.11	0.03	23.28
Male	Left grip	−0.28	0.17	1.41	−20.59
	Right grip	−0.27	0.19	1.65	−32.94
	Left elbow flexion	−0.14	0.15	0.24	26.61
	Right elbow flexion	−0.17	0.16	0.53	5.89
	Left elbow extension	−0.26	0.14	−0.21	50.13
	Right elbow extension	−0.29	0.13	−0.24	55.17
	Left knee extension	−0.011	0.297	−0.594	74.789
	Right knee extension	0.022	0.33	−1.056	101.992
	Left knee flexion	−0.19	0.18	0.27	−1.07
	Right knee flexion	−0.22	0.16	0.15	14.26
	Left ankle dorsiflexion	−0.06	0.11	0.06	26.03
	Right ankle dorsiflexion	−0.04	0.13	0.02	26.62

*Coefficients and intercepts were modified from the originally published values, as necessary, based on use of ATLIS Version 2.

For example, the predicted value for the left grip maneuver for a 41-year-old woman who is 62 inches tall and weighs 126 pounds would be calculated as follows:

$$Predicted = -28.91 - 0.15*Age + 0.16*Weight + 1.18*Height$$

$$Predicted = -28.91 - 0.15*41 + 0.16*126 + 1.18*62$$

$$Predicted = 58.26$$

2. For each of the 12 muscle groups, a standardized ATLIS score was calculated by dividing the maximum observed score for each participant and visit combination by the predicted score. If a participant had no motion in a limb and could thus not be tested, the participant's observed score was recorded as 0 (translating to a standardized score of 0 as well). If a participant had motion in a limb but was unable to complete the testing for some other reason, these data were considered missing.
3. The ATLIS upper-limb score was obtained by averaging the six standardized upper muscle groups (left grip, right grip, left elbow flexion, right elbow flexion, left elbow extension, right elbow extension). The average score was calculated only if at least four of the six items were observed.
4. The ATLIS lower-limb score was obtained by averaging the six standardized lower muscle groups (left knee extension, right knee extension, left knee flexion, right knee flexion, left ankle dorsiflexion, right ankle dorsiflexion). The average score was calculated only if at least four of the six items were observed.
5. The ATLIS total score was obtained by averaging the ATLIS upper- and lower-limb scores (numbers 3 and 4 above); both upper- and lower-limb scores were required to make this calculation.

The analysis used the highest score from all attempts of a given maneuver at each assessment.

Section 3.4. Outcomes Evaluator Specifications

All ALSFRS-R and SVC evaluators were NEALS certified. ATLIS evaluators received training from a core group of four experienced physical therapists and were required to demonstrate competency and consistency in obtaining measurements. The trial protocol specified that the same evaluator should perform all assessments in each participant throughout the trial, if possible. All evaluators were blinded to treatment.

Section 3.5. Detailed Statistical Methods

Confirmation of Linear Assumption in Primary ALSFRS-R Analysis

To analyze potential nonlinearity in ALSFRS-R progression, the analysis plan included testing a model that included quadratic terms for time since baseline and for key covariates. In the analysis plan, if the quadratic term for time was found to have significance ($P<0.10$), then a quadratic model would be used instead of the linear model. However, the quadratic term for time was not significant ($P>0.10$) for the primary and secondary outcomes; therefore, only linear terms were retained for the final analysis.

Sensitivity Analyses: Missing Data, Intercurrent Events, and Time on Concomitant Medications

Three sensitivity models were performed to assess the impact of missing data, and three additional sensitivity models were performed to assess the impact of concomitant medications. (See Fig. S3 for results of these analyses.) The first sensitivity model was a post hoc joint rank model in the safety population that incorporated all survival events into the analysis of function (ALSFRS-R), providing adjusted estimates that accounted for potential bias due to participant death.[8] The model ranked participants by time to death and then by change in ALSFRS-R total

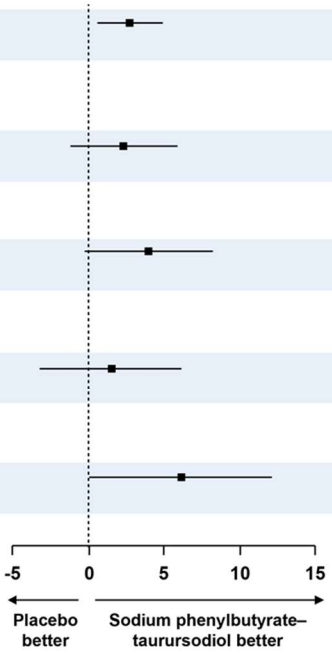
score. This ranked score was then analyzed as the outcome of an analysis of covariance model that included the same covariates as the primary model, but replaced the covariates with ranked covariates. The other two prespecified sensitivity models for missing data were based on creating datasets with imputed data. The first model imputed a lower value than previous scores for each participant who died and is referred to as the Post-Death Imputation Model. The second model imputed missing data for all participants who discontinued for any reason and is referred to as the Multiple Imputation Model for MNAR. For this model, the imputed values for the placebo arm were imputed on their linear trajectory (with error), and imputed values for the active arm were imputed on their linear trajectory after subtracting out the difference in average slope between the active and placebo groups.

Three prespecified sensitivity models were used to assess the effect of concomitant use of riluzole, edaravone, or both on efficacy outcomes. The primary efficacy model was used as a basis for all three models, and terms were added to account for time on either concomitant medication or both. Interaction terms between treatment and concomitant medication use were assessed for positive or negative synergy. There was no evidence of synergistic effects for any of these three models.

4. Supplementary Figures

Figure S1. Change-From-Baseline Analysis for Continuous Outcomes.

The primary analysis for all continuous outcomes was a random-slope linear mixed model (adjusted for age and pre-baseline ALSFRS-R slope) comparing slopes between active and placebo groups using the absolute score at each visit. A change-from-baseline analysis comparing slopes was performed post hoc for all continuous outcomes in the mITT population. *Only significant P values are reported per prespecified hierarchical order of outcomes. Maximum *absolute* ALSFRS-R total score=48.[9]



		Sodium Phenylbutyrate–Taurursodiol (n=87)	Placebo (n=48)	Adjusted Difference (SE), Active Minus Placebo [95% CI]	P Value*
Primary					
ALSFRS-R total score	Mean (SE) change from baseline to week 24	-6.70 (0.68)	-9.62 (0.910)	2.92 (1.31) [0.70, 5.15]	0.01
	Mean (SE) change per month	-1.21 (0.12)	-1.74 (0.16)	0.53 (0.21) [0.13, 0.93]	
***Secondary (Clinical)* — % of predicted normal value**					
ATLIS total score	Mean (SE) change from baseline to week 24	-16.91 (1.13)	-19.41 (1.52)	2.50 (1.87) [-1.18, 6.17]	
	Mean (SE) change per month	-3.06 (0.20)	-3.52 (0.28)	0.45 (0.34) [-0.21, 1.12]	
ATLIS upper-limb score	Mean (SE) change from baseline to week 24	-16.91 (1.34)	-21.07 (1.81)	4.16 (2.22) [-0.21, 8.54]	
	Mean (SE) change per month	-3.06 (0.24)	-3.82 (0.33)	0.75 (0.40) [-0.04, 1.55]	
ATLIS lower-limb score	Mean (SE) change from baseline to week 24	-16.72 (1.47)	-18.27 (1.98)	1.55 (2.42) [-3.21, 6.31]	
	Mean (SE) change per month	-3.03 (0.27)	-3.31 (0.36)	0.28 (0.44) [-0.58, 1.14]	
SVC	Mean (SE) change from baseline to week 24	-17.20 (1.86)	-23.54 (2.51)	6.34 (3.08) [0.28, 12.39]	
	Mean (SE) change per month	-3.12 (0.34)	-4.27 (0.45)	1.15 (0.558) [0.05, 2.25]	

Figure S2. Estimated Rate of Decline in ALSFRS-R Total Score Over 24 Weeks.

The figure shows the treatment-dependent rates of decline in ALSFRS-R total score estimated in the mITT population in the primary analysis (red = sodium phenylbutyrate–taurursodiol, green = placebo; shading reflects plus and minus one standard error). Overlaid on the estimated slopes from the primary analysis are visit-specific estimates (and standard error bars) from a post hoc shared-baseline, repeated-measures mixed model with the same adjustments but categorical time and unstructured covariance among repeated measures.

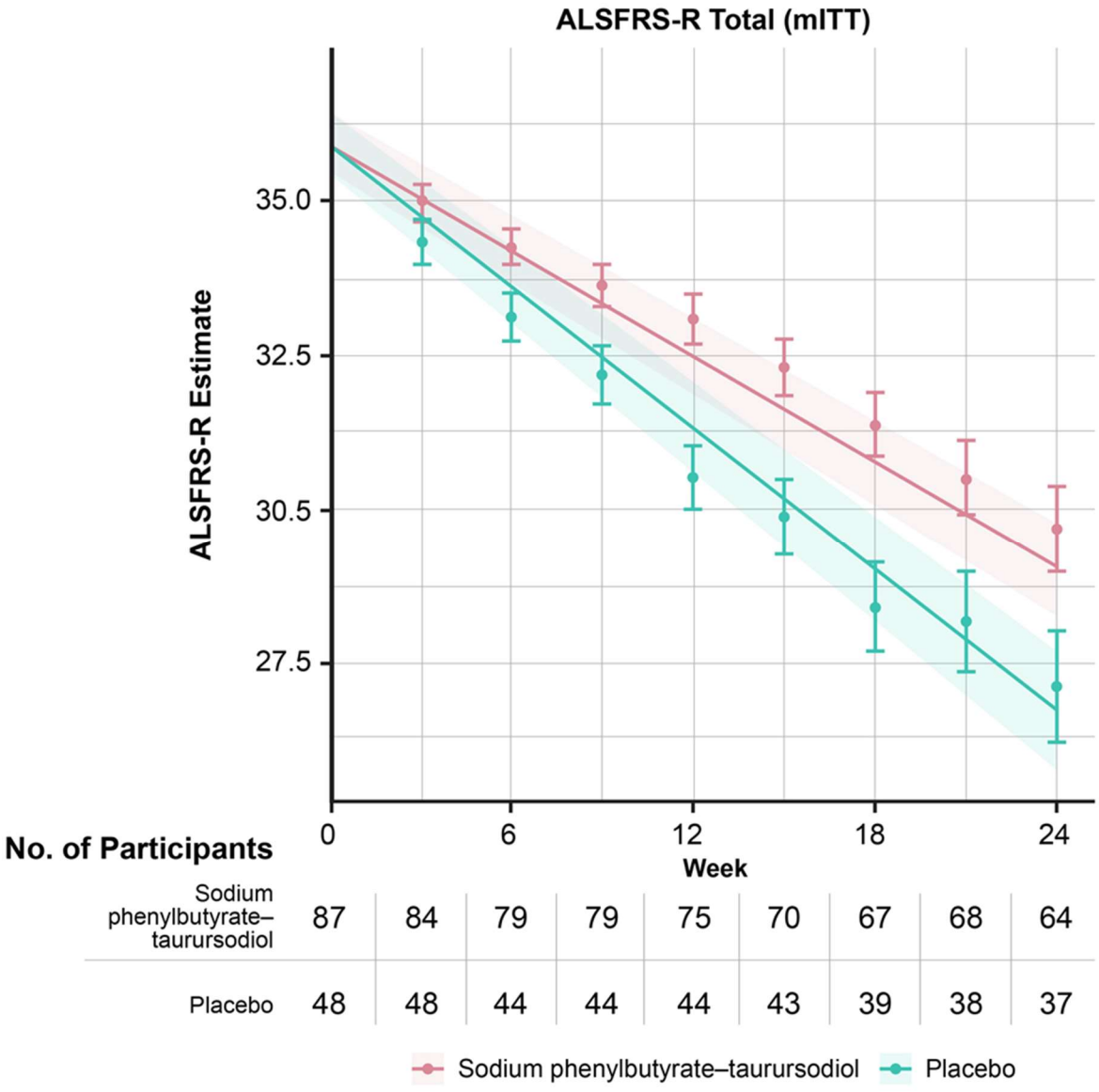
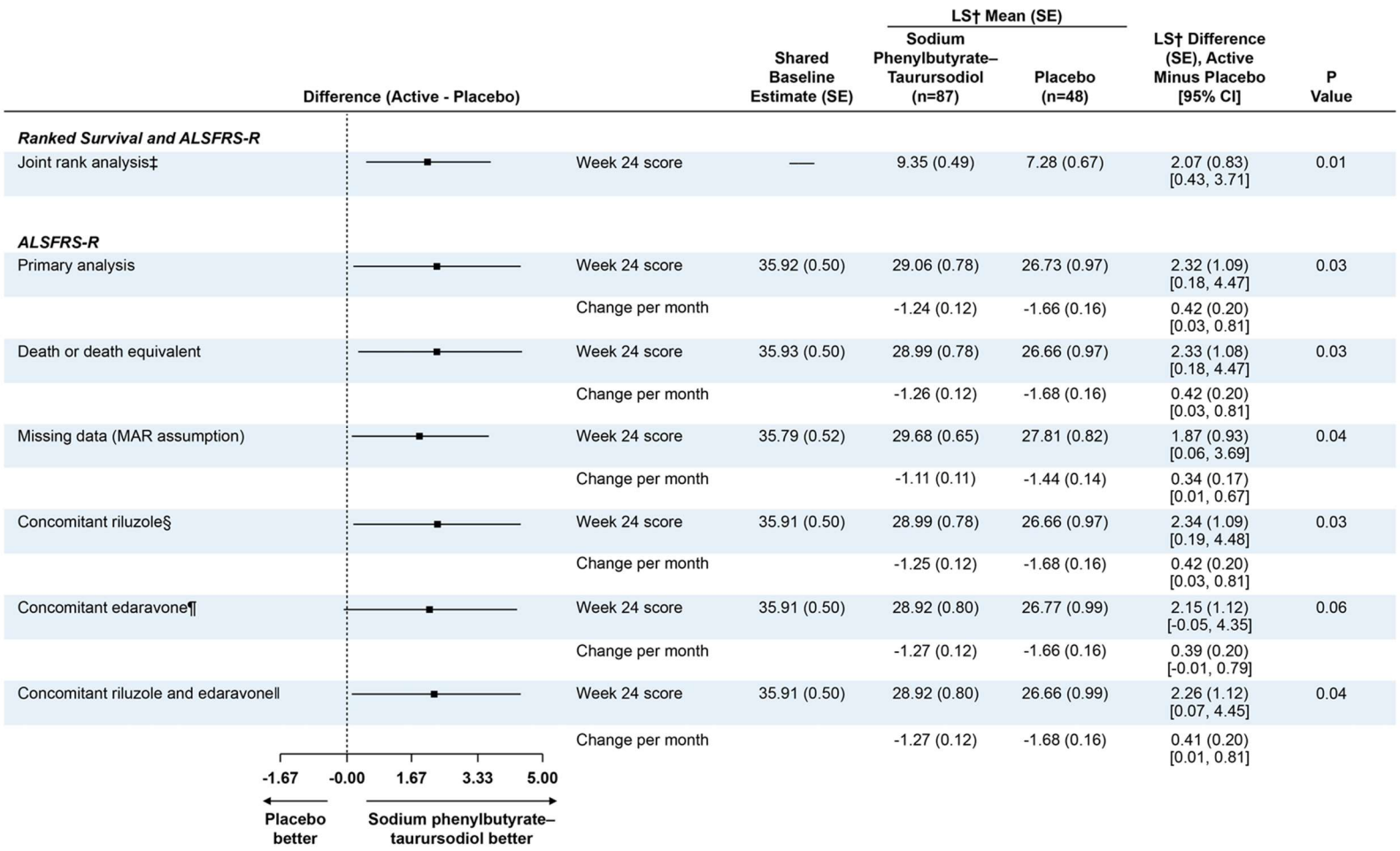


Figure S3. Sensitivity Analyses: Joint Rank, Missing Data, Intercurrent Events, and Time on Concomitant Medications.*

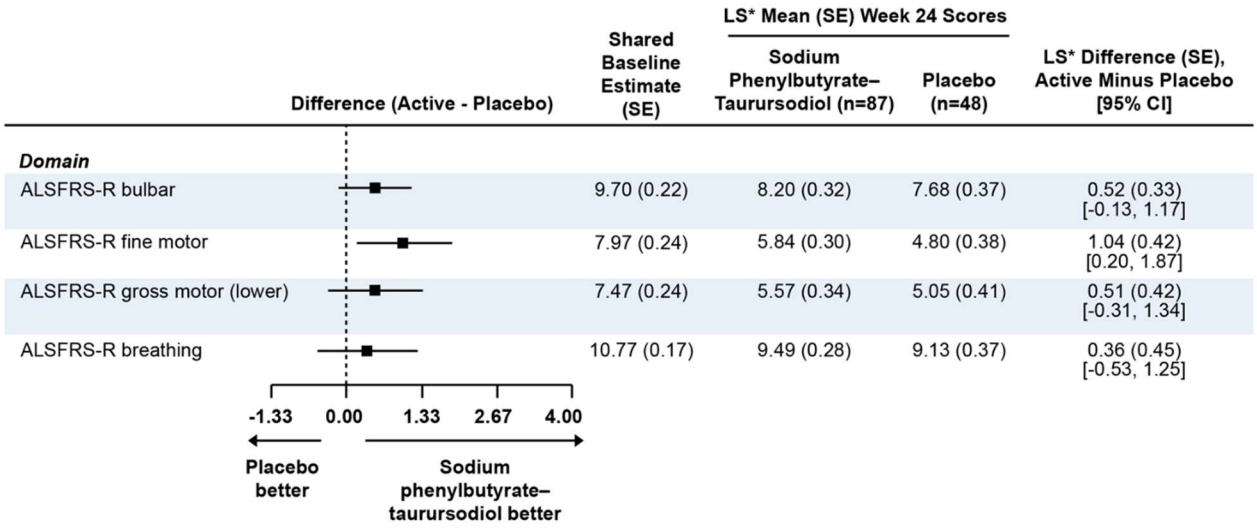
*mITT population. †LS denotes a mean or difference adjusted for terms in the model. ‡The joint rank analysis results are reported here as the rank divided by 8 so that results would be on a similar scale as those being presented for ALSFRS-R. §Mean weeks on riluzole = 17.86. ¶Mean weeks on edaravone = 10.50. ‖Mean weeks on riluzole and edaravone = 8.79.



		Shared Baseline Estimate (SE)	LS† Mean (SE) Sodium Phenylbutyrate–Taurursodiol (n=87)	LS† Mean (SE) Placebo (n=48)	LS† Difference (SE), Active Minus Placebo [95% CI]	P Value
Ranked Survival and ALSFRS-R						
Joint rank analysis‡	Week 24 score	—	9.35 (0.49)	7.28 (0.67)	2.07 (0.83) [0.43, 3.71]	0.01
ALSFRS-R						
Primary analysis	Week 24 score	35.92 (0.50)	29.06 (0.78)	26.73 (0.97)	2.32 (1.09) [0.18, 4.47]	0.03
	Change per month		-1.24 (0.12)	-1.66 (0.16)	0.42 (0.20) [0.03, 0.81]	
Death or death equivalent	Week 24 score	35.93 (0.50)	28.99 (0.78)	26.66 (0.97)	2.33 (1.08) [0.18, 4.47]	0.03
	Change per month		-1.26 (0.12)	-1.68 (0.16)	0.42 (0.20) [0.03, 0.81]	
Missing data (MAR assumption)	Week 24 score	35.79 (0.52)	29.68 (0.65)	27.81 (0.82)	1.87 (0.93) [0.06, 3.69]	0.04
	Change per month		-1.11 (0.11)	-1.44 (0.14)	0.34 (0.17) [0.01, 0.67]	
Concomitant riluzole§	Week 24 score	35.91 (0.50)	28.99 (0.78)	26.66 (0.97)	2.34 (1.09) [0.19, 4.48]	0.03
	Change per month		-1.25 (0.12)	-1.68 (0.16)	0.42 (0.20) [0.03, 0.81]	
Concomitant edaravone¶	Week 24 score	35.91 (0.50)	28.92 (0.80)	26.77 (0.99)	2.15 (1.12) [-0.05, 4.35]	0.06
	Change per month		-1.27 (0.12)	-1.66 (0.16)	0.39 (0.20) [-0.01, 0.79]	
Concomitant riluzole and edaravone‖	Week 24 score	35.91 (0.50)	28.92 (0.80)	26.66 (0.99)	2.26 (1.12) [0.07, 4.45]	0.04
	Change per month		-1.27 (0.12)	-1.68 (0.16)	0.41 (0.20) [0.01, 0.81]	

Figure S4. ALSFRS-R Subdomain Scores.

*Least squares (LS) denotes a mean or difference adjusted for terms in the model. Maximum score for each subdomain is 12 points.[9]



Domain	Shared Baseline Estimate (SE)	LS* Mean (SE) Week 24 Scores: Sodium Phenylbutyrate–Taurursodiol (n=87)	LS* Mean (SE) Week 24 Scores: Placebo (n=48)	LS* Difference (SE), Active Minus Placebo [95% CI]
ALSFRS-R bulbar	9.70 (0.22)	8.20 (0.32)	7.68 (0.37)	0.52 (0.33) [-0.13, 1.17]
ALSFRS-R fine motor	7.97 (0.24)	5.84 (0.30)	4.80 (0.38)	1.04 (0.42) [0.20, 1.87]
ALSFRS-R gross motor (lower)	7.47 (0.24)	5.57 (0.34)	5.05 (0.41)	0.51 (0.42) [-0.31, 1.34]
ALSFRS-R breathing	10.77 (0.17)	9.49 (0.28)	9.13 (0.37)	0.36 (0.45) [-0.53, 1.25]

Figure S5. Secondary Outcomes Results: ATLIS and SVC.

Panels A through C show the treatment-dependent rates of decline in ATLIS total, upper-limb, and lower-limb ATLIS scores, respectively, while panel D shows similar results for SVC (red = sodium phenylbutyrate–taurursodiol, green = placebo; shading reflects plus and minus one standard error) in the mITT population. Overlaid on the estimated slopes from the primary analyses are visit-specific estimates (and standard error bars) from a post hoc shared-baseline, repeated-measures mixed model with the same adjustments but categorical time and unstructured covariance among repeated measures.

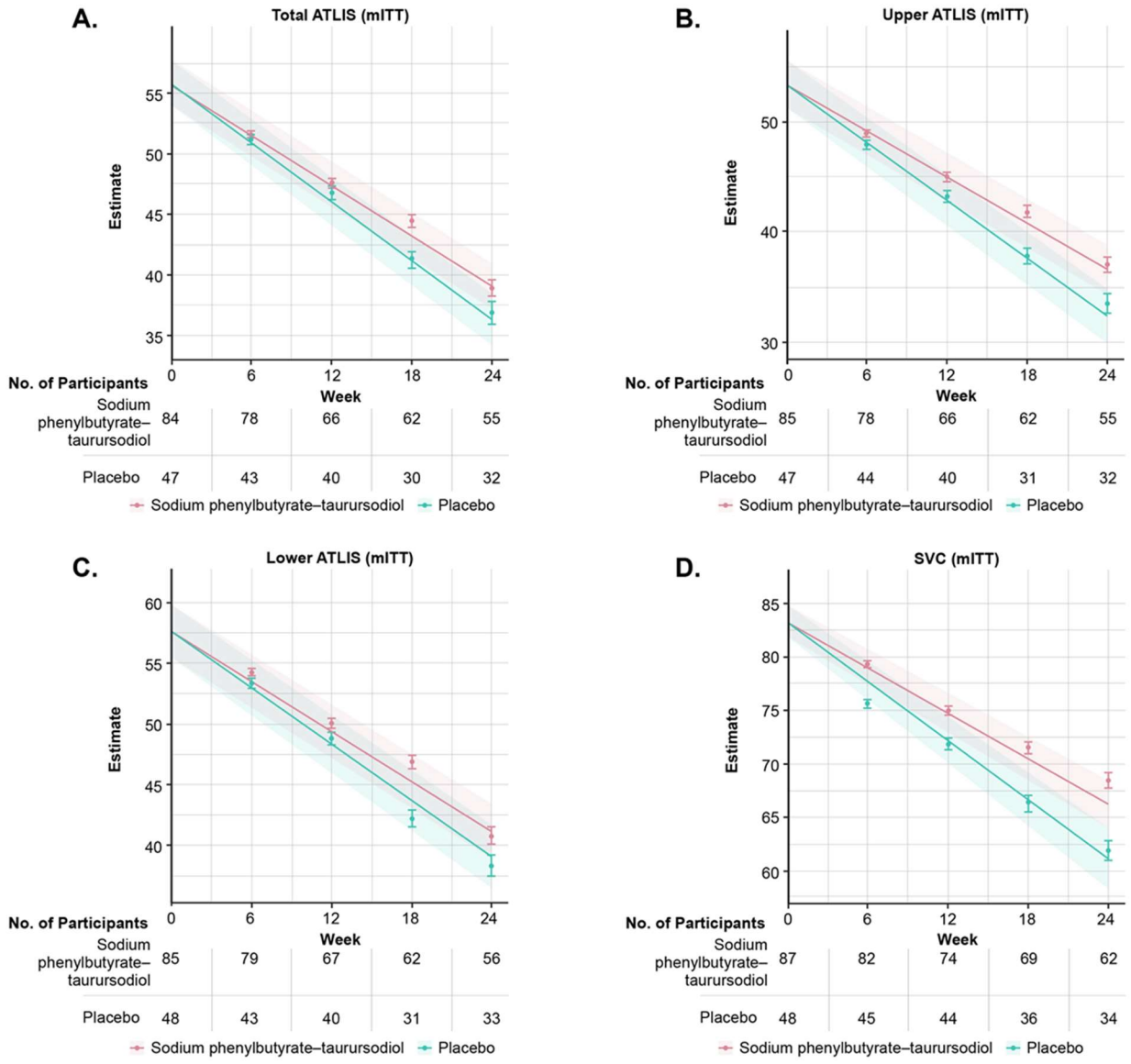


Figure S6. Kaplan-Meier Plot of Cumulative Death, Tracheostomy, and Hospitalization Events.

The composite outcome was defined as death, a death-equivalent event (which consisted of only tracheostomy in one participant in this trial), or hospitalization, whichever occurred first; there were no instances of permanent ventilation delivered by noninvasive means in the study. Survival status was obtained for all participants at their respective week 24 visits; therefore, none of the data presented in the figure are censored due to lost-to-follow-up. A test of the Schoenfeld residuals was performed to test the null hypothesis of the proportional hazards for survival. The P values for the global and individual tests were 0.37 and 0.50, respectively, providing no evidence against proportional hazards.

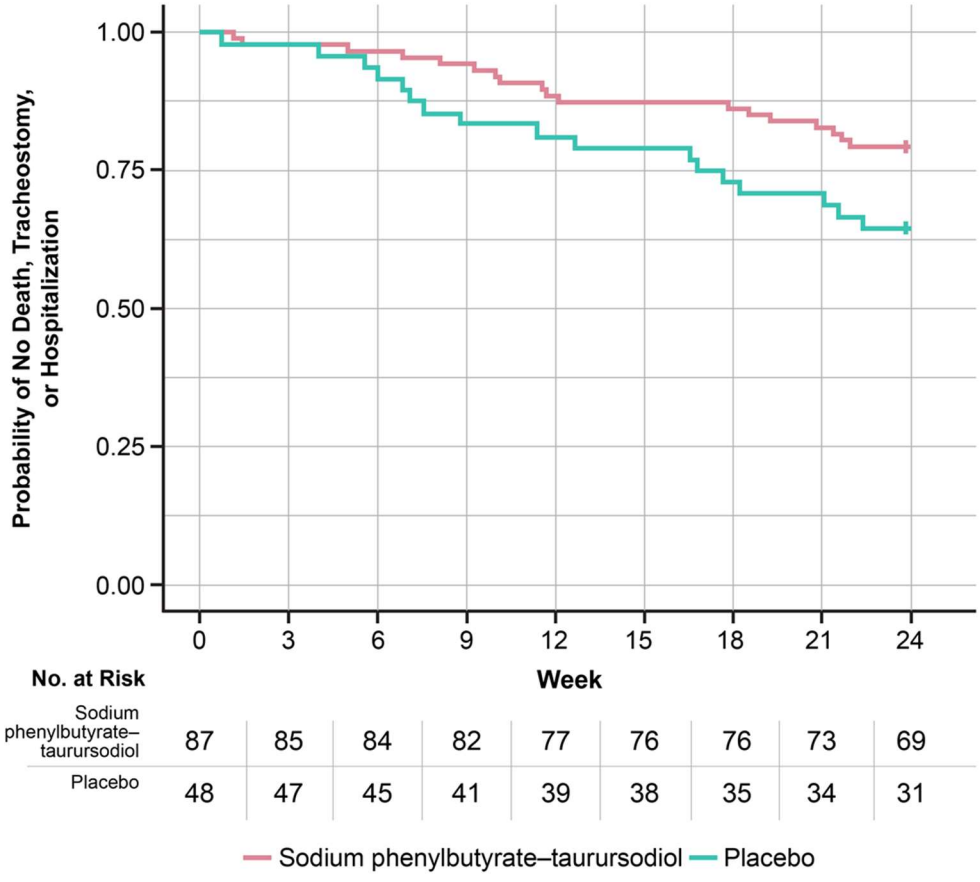
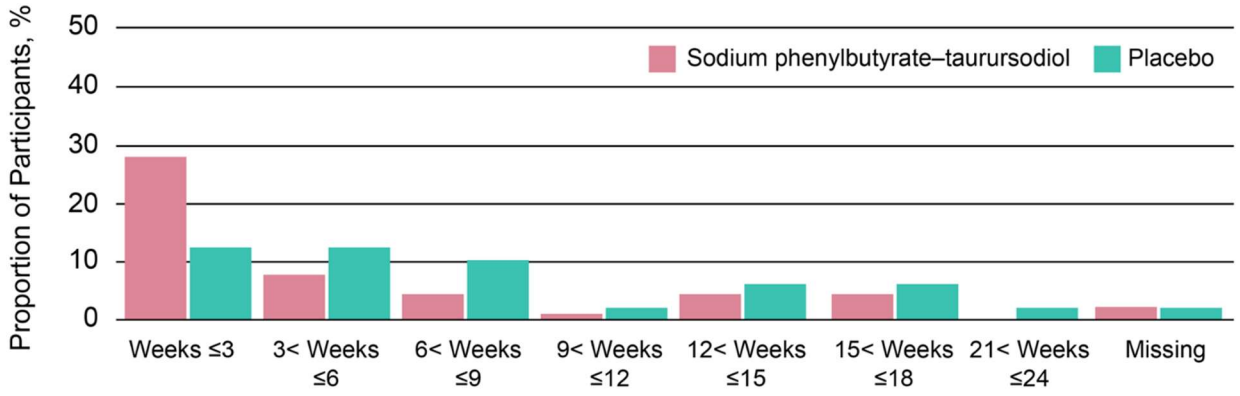


Figure S7. Incidence of Gastrointestinal Adverse Events by Trial Week.

The incidence of gastrointestinal adverse events peaked in sodium phenylbutyrate–taurursodiol group in the first 3 weeks of the trial, declining thereafter to below that observed in the placebo group for the remainder of the trial.



5. Supplementary Tables

Table S1. Schedule of Trial Visits and Assessments

ACTIVITY	Screening Visit	Trial Drug Administration (weeks)									Final Follow-up Telephone Call[b]	MR-PET Sub-Trial Participants Only
		Baseline Visit[a]	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18	Week 21	Week 24 OR Early Discontinuation/ Final Safety Visit		
	Clinic	Clinic	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Clinic	Phone	At MGH
	-42 Days	Day 0	Day 21 ±5	Day 42 ±5	Day 63 ±5	Day 84 ±5	Day 105 ±5	Day 126 ±5	Day 147 ±5	Day 168 ±5	28 +5 days	
Written informed consent	X											X
Inclusion/exclusion review	X	X										X
Medical history/demographics	X											
ALS diagnosis/ALS history	X											
Vital signs[c]	X	X	X	X		X		X		X		
Neurological examination[d]	X					X				X		X[d]
Physical examination[e]	X					X				X		
Blood draw for safety labs[f]	X	X	X	X		X		X		X		
Blood draw for serum pregnancy test for WOCBP[f]	X											
Urine sample for urinalysis[f]	X	X	X	X		X		X		X		
12-Lead ECG	X					X				X		
ALSFRS-R	X	X	X	X	X	X	X	X	X	X	X	X
SVC	X	X		X		X		X		X		
ATLIS testing	X	X		X		X		X		X		
C-SSRS[g]		X[g]	X	X		X		X		X		
Exit questionnaire										X		
MR-PET scan[h]		X				X						X[h]
Blood draw for biomarker testing[i]		X		X		X		X		X		
Blood draw for PK analysis[j]		X				X				X[k]		
Blood draw for optional DNA collection[l]		X	X	X		X		X		X		
Adverse events[m]	X	X	X	X	X	X	X	X	X	X	X	X
Blood draw for TSPO affinity testing[n]	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[o]		X										
Dispense trial drug[p]		X		X		X		X				
Drug accountability/ compliance			X[q]	X	X	X	X	X	X	X		

[a]The baseline visit was set to occur no more than 42 days after the screening visit.

[b]A final safety telephone call was conducted 28 (+5 days) after the participant took their last dose of trial drug (whether or not the participant discontinued from the trial) to assess for adverse events and changes in concomitant medications and to administer the ALSFRS-R. This call was only required for participants who did not enroll in the OLE.
[c]Vital signs included systolic and diastolic pressure in mm Hg, respiratory rate/minute, heart rate/minute, and temperature.
[d] The standard neurological examination was used for all participants. The Upper Motor Neuron Burden Scale was included for the MR-PET sub-trial only and administered at the time of the scan.
[e]Physical examination included height and weight. Height was measured at the screening visit only.
[f]Safety labs included hematology (CBC with differential), complete chemistry panel, liver function tests, and urinalysis. Serum pregnancy testing was performed in WOCBP at the screening visit and as necessary during the course of the trial.
[g]C-SSRS Baseline version was completed at baseline visit only. C-SSRS Since Last Visit version was completed at all other visits.
[h]Approximately 20 participants underwent MR-PET scanning at selected sites. The first scan occurred prior to the baseline visit (pre-dose), and the second scan occurred between the week 12 and week 21 trial visits. Participants who underwent MR-PET also provided blood samples for peripheral blood mononuclear cell extraction prior to each MR-PET scan.
[i]Participants provided a blood sample for biomarker testing and storage in a biorepository.
[j]All participants provided a blood sample for PK testing at the baseline visit (pre-dose). Participants also provided a blood sample either 1 hour or 4 hours post-dose (±10-minute window per time point) at the week 12 and week 24 Visits. PK times were randomized such that every participant had a 1-hour draw at one visit and a 4-hour draw at the other.
[k]PK sample was not drawn for participants who terminated early.
[l] If the baseline visit had already occurred or the sample was not collected, DNA was obtained at the next available visit. This was a one-time collection.
[m]Adverse events that occurred after signing the consent form were recorded.
[n]For participants in the MR-PET sub-trial only, blood was drawn for TSPO testing at the participant's site during the screening visit.
[o]Randomization occurred at the baseline visit. Randomization entailed entering a participant's kit number into the data capture system.
[p]The first dose of trial drug was administered in clinic after all baseline visit procedures were completed.
[q]Subjects were directed to increase from one sachet per day to two sachets per day, if tolerated.

Table S2. Trial Drug Adherence

Trial drug adherence was assessed by having participants return their empty and unused sachets at each clinic visit. Adherence was defined as taking more than 80% or less than 125% of anticipated trial drug as determined by sachet counts.

Parameter*	Sodium Phenylbutyrate–Taurursodiol (n=89)	Placebo (n=48)
Adherence†— %	90.1±19.3	90.2±15.7

*Means ± SD. †Adherence is calculated as the number of empty sachets returned / total number of sachets (empty + unused).

Table S3. Post Hoc ITT Primary and Secondary Outcome Analyses

To support the primary mITT analysis in CENTAUR, a post hoc ITT analysis, including two participants in the active group who did not undergo a post-baseline efficacy assessment and were thus excluded from the mITT population, was performed. The ITT analysis yielded results that were identical within rounding error to the primary mITT analysis. Secondary outcomes were also identical within rounding error for the ITT and mITT analyses, with the exception of the survival analysis, for which the ITT analysis included the participants in the sodium phenylbutyrate–taurursodiol group who died soon after randomization. *Least squares (LS) denotes a mean or difference adjusted for terms in the model. †Only significant P values are reported per prespecified hierarchical order of outcomes. (Table continued on next page.)

Outcome	Shared Baseline Estimate (SE)	LS* Mean (SE)		LS* Difference (SE), Active Minus Placebo [95% CI]	P Value†
		Sodium Phenylbutyrate–Taurursodiol (n=89)	Placebo (n=48)		
Primary					
ALSFRS-R total score					
Week 24 score	35.88 (0.50)	29.01 (0.78)	26.68 (0.97)	2.32 (1.09) [0.18, 4.47]	0.03
Change per month		-1.24 (0.12)	-1.67 (0.16)	0.42 (0.20) [0.03, 0.81]	
Secondary (Continuous) — % of predicted normal value					
ATLIS total score					
Week 24 score	55.56 (1.78)	38.84 (1.98)	36.02 (2.21)	2.82 (1.77) [-0.67, 6.31]	
Change per month		-3.03 (0.19)	-3.54 (0.26)	0.51 (0.32) [-0.12, 1.14]	
ATLIS upper-limb score					
Week 24 score	53.42 (2.12)	36.62 (2.29)	32.35 (2.57)	4.27 (2.09) [0.16, 8.38]	
Change per month		-3.04 (0.23)	-3.82 (0.31)	0.77 (0.38) [0.03, 1.52]	
ATLIS lower-limb score					
Week 24 score	57.17 (2.20)	40.72 (2.36)	38.64 (2.66)	2.09 (2.19) [-2.23, 6.40]	
Change per month		-2.98 (0.240)	-3.36 (0.326)	0.38 (0.398) [-0.40, 1.16]	
SVC					
Week 24 percentage	82.70 (1.57)	65.54 (2.35)	60.45 (2.83)	5.10 (2.87) [-0.55, 10.74]	
Change per month		-3.11 (0.31)	-4.03 (0.42)	0.92 (0.52) [-0.10, 1.95]	

Outcome	Sodium Phenylbutyrate–Taurursodiol (n=89)	Placebo (n=48)	Hazard Ratio, Active Minus Placebo [95% CI]
Secondary (Survival)			
Death, tracheostomy, or hospitalization			
Estimated percentage (SE) of event	20.7 (4.31)	32.8 (6.86)	0.58 [0.30, 1.14]
Death or tracheostomy			
Estimated percentage (SE) of event	3.8 (2.07)	4.3 (2.84)	0.89 [0.20, 4.75]
Hospitalization			
Estimated percentage (SE) of event	18.0 (4.09)	29.9 (6.63)	0.56 [0.29, 1.14]

Table S4. Treatment-Emergent Adverse Events*

MedDRA SOC Preferred Term	Incidence — no. (%)	
	Sodium Phenylbutyrate–Taurursodiol (n=89)	Placebo (n=48)
Gastrointestinal disorders	60 (67)	29 (60)
Diarrhea†	19 (21)	9 (19)
Constipation‡	13 (15)	11 (23)
Nausea†	17 (19)	6 (12)
Abdominal pain†	7 (8)	3 (6)
Salivary hypersecretion†	9 (10)	1 (2)
Dry mouth‡	3 (3)	4 (8)
Abdominal pain upper†	5 (6)	1 (2)
Abdominal discomfort†	5 (6)	0
Abdominal distention†	4 (5)	1 (2)
Dysphagia‡	2 (2)	3 (6)
Vomiting†	4 (4)	1 (2)
Flatulence	3 (3)	1 (2)
Dyspepsia†	3 (3)	0
Gastroesophageal reflux disease	2 (2)	1 (2)
Aphthous ulcer†	2 (2)	0
Gastrointestinal hypermotility†	2 (2)	0
Retching†	2 (2)	0
Change of bowel habit	1 (1)	0
Epigastric discomfort	1 (1)	0
Eructation‡	0	1 (2)
Feces soft	1 (1)	0
Frequent bowel movements‡	0	1 (2)
Hypertrophy of tongue papillae	1 (1)	0
Impaired gastric emptying	1 (1)	0
Irritable bowel syndrome	1 (1)	0
Pneumoperitoneum	1 (1)	0
Stomatitis‡	0	1 (2)
Tooth discoloration	1 (1)	0
Toothache	1 (1)	0
Musculoskeletal and connective tissue disorders	38 (43)	21 (44)
Muscular weakness‡	16 (18)	11 (23)
Back pain	6 (7)	4 (8)
Muscle spasms	5 (6)	3 (6)
Arthralgia†	5 (6)	2 (4)
Musculoskeletal pain†	5 (6)	2 (4)
Neck pain‡	2 (2)	5 (10)
Musculoskeletal chest pain†	5 (6)	1 (2)
Pain in extremity†	4 (4)	0
Limb discomfort	2 (2)	1 (2)
Myalgia	2 (2)	1 (2)
Mobility decreased	1 (1)	1 (2)
Muscle twitching	2 (2)	0
Extremity contracture‡	0	1 (2)
Joint swelling	1 (1)	0
Musculoskeletal discomfort‡	0	1 (2)
Musculoskeletal stiffness	1 (1)	0
Spinal pain	1 (1)	0
Injury, poisoning, and procedural complications	35 (39)	23 (48)
Fall‡	29 (33)	19 (40)
Contusion	8 (9)	4 (8)
Laceration‡	5 (6)	5 (10)

Stoma site pain	3 (3)	2 (4)
Rib fracture†	3 (3)	0
Skin abrasion‡	1 (1)	2 (4)
Humerus fracture†	2 (2)	0
Ligament sprain‡	0	2 (4)
Limb injury	1 (1)	1 (2)
Tooth fracture	1 (1)	1 (2)
Concussion	1 (1)	0
Extradural hematoma‡	0	1 (2)
Eye contusion	1 (1)	0
Hand fracture	1 (1)	0
Ligament rupture	1 (1)	0
Muscle strain‡	0	1 (2)
Pelvic fracture‡	0	1 (2)
Post-concussion syndrome	1 (1)	0
Procedural complication	1 (1)	0
Skull fracture	1 (1)	0
Stoma site hemorrhage	1 (1)	0
Subdural hematoma	1 (1)	0
Sunburn	1 (1)	0
Thermal burn	1 (1)	0
Traumatic hematoma	1 (1)	0
Nervous system disorders	33 (37)	19 (40)
Headache‡	12 (14)	10 (21)
Dizziness†	11 (12)	3 (6)
Dysarthria	3 (3)	2 (4)
Dysgeusia	3 (3)	1 (2)
Muscle contractions involuntary	3 (3)	1 (2)
Hypoesthesia	2 (2)	1 (2)
Somnolence†	3 (3)	0
Speech disorder†	3 (3)	0
Syncope‡	1 (1)	2 (4)
Tremor	2 (2)	1 (2)
Balance disorder†	2 (2)	0
Depressed level of consciousness	1 (1)	1 (2)
Paresthesia	1 (1)	1 (2)
Amyotrophic lateral sclerosis	1 (1)	0
Burning sensation	1 (1)	0
Lethargy	1 (1)	0
Migraine	1 (1)	0
Muscle spasticity‡	0	1 (2)
Restless legs syndrome‡	0	1 (2)
Infections and infestations	28 (32)	21 (44)
Viral upper respiratory tract infection†	11 (12)	4 (8)
Urinary tract infection†	7 (8)	3 (6)
Upper respiratory tract infection‡	4 (4)	3 (6)
Fungal infection‡	1 (1)	2 (4)
Influenza‡	1 (1)	2 (4)
Pneumonia	2 (2)	1 (2)
Sinusitis	2 (2)	1 (2)
Acute sinusitis	1 (1)	0
Bacteremia‡	0	1 (2)
Candida infection	1 (1)	0
Catheter site infection	1 (1)	0
Cellulitis	1 (1)	0
Diverticulitis	1 (1)	0
Gastroenteritis viral‡	0	1 (2)
Hordeolum‡	0	1 (2)
Implant site infection‡	0	1 (2)

Incision site infection	1 (1)	0
Localized infection	1 (1)	0
Lower respiratory tract infection‡	0	1 (2)
Lyme disease‡	0	1 (2)
Nematodiasis‡	0	1 (2)
Pharyngitis streptococcal	1 (1)	0
Postoperative wound infection	1 (1)	0
Tooth abscess	1 (1)	0
Viral infection	1 (1)	0
Wound infection‡	0	1 (2)
Respiratory, thoracic, and mediastinal disorders	29 (33)	10 (21)
Dyspnea†	9 (10)	3 (6)
Respiratory failure	5 (6)	3 (6)
Cough‡	4 (4)	3 (6)
Choking	2 (2)	1 (2)
Sputum increased	2 (2)	1 (2)
Nasal congestion†	2 (2)	0
Oropharyngeal pain†	2 (2)	0
Respiratory tract congestion‡	0	2 (4)
Throat irritation†	2 (2)	0
Asthma	1 (1)	0
Atelectasis‡	0	1 (2)
Diaphragmatic disorder‡	0	1 (2)
Diaphragmatic spasm	1 (1)	0
Dyspnea exertional	1 (1)	0
Epistaxis	1 (1)	0
Hypoxia‡	0	1 (2)
Orthopnea	1 (1)	0
Pleural effusion‡	0	1 (2)
Pneumonia aspiration	1 (1)	0
Productive cough	1 (1)	0
Pulmonary embolism‡	0	1 (2)
Sinus congestion	1 (1)	0
Sneezing	1 (1)	0
Upper-airway cough syndrome‡	0	1 (2)
Wheezing‡	0	1 (2)
Investigations	26 (29)	10 (21)
Alanine aminotransferase increased‡	4 (4)	4 (8)
Aspartate aminotransferase increased‡	4 (4)	3 (6)
Weight decreased†	6 (7)	1 (2)
Crystal urine present†	4 (4)	0
Protein urine‡	2 (2)	2 (4)
Blood glucose increased†	3 (3)	0
Hematocrit increased	2 (2)	1 (2)
Mean cell volume abnormal	2 (2)	1 (2)
Blood creatinine increased†	2 (2)	0
Platelet count increased‡	0	2 (4)
Transaminases increased†	2 (2)	0
Urine ketone body	1 (1)	1 (2)
Blood bilirubin increased	1 (1)	0
Blood potassium decreased	1 (1)	0
Blood potassium increased‡	0	1 (2)
Blood pressure increased‡	0	1 (2)
Blood urine	1 (1)	0
Blood urine present	1 (1)	0
Heart rate increased‡	0	1 (2)
Mean cell volume increased	1 (1)	0
Monocyte count increased	1 (1)	0
Neutrophil count increased	1 (1)	0

Red blood cell microcytes‡	0	1 (2)
Red blood cells urine positive	1 (1)	0
Respiratory syncytial virus test positive	1 (1)	0
Urine leukocyte esterase positive	1 (1)	0
General disorders and administration site conditions	20 (22)	13 (27)
Fatigue†	9 (10)	3 (6)
Edema peripheral‡	3 (3)	3 (6)
Asthenia†	5 (6)	0
Pyrexia	3 (3)	1 (2)
Chest pain†	2 (2)	0
Disease progression‡	0	2 (4)
Pain	1 (1)	1 (2)
Catheter site thrombosis	1 (1)	0
Chills	1 (1)	0
Feeling abnormal	1 (1)	0
Gait disturbance‡	0	1 (2)
Infusion site bruising‡	0	1 (2)
Peripheral swelling‡	0	1 (2)
Secretion discharge‡	0	1 (2)
Swelling	1 (1)	0
Skin and subcutaneous tissue disorders	16 (18)	8 (17)
Rash‡	5 (6)	4 (8)
Decubitus ulcer	3 (3)	1 (2)
Skin odor abnormal†	3 (3)	0
Pruritus	1 (1)	1 (2)
Acne‡	0	1 (2)
Dermatitis contact	1 (1)	0
Dry skin	1 (1)	0
Eczema‡	0	1 (2)
Erythema	1 (1)	0
Hyperhidrosis	1 (1)	0
Petechiae‡	0	1 (2)
Pruritus generalized‡	0	1 (2)
Rash erythematous	1 (1)	0
Seborrhea	1 (1)	0
Psychiatric disorders	14 (16)	9 (19)
Insomnia‡	2 (2)	3 (6)
Affect lability‡	2 (2)	2 (4)
Anxiety‡	2 (2)	2 (4)
Depression	3 (3)	1 (2)
Adjustment disorder with depressed mood	1 (1)	0
Agitation	1 (1)	0
Anger	1 (1)	0
Depressed mood‡	0	1 (2)
Euphoric mood	1 (1)	0
Hallucination, visual	1 (1)	0
Panic attack‡	0	1 (2)
Sleep order	1 (1)	0
Suicidal ideation	1 (1)	0
Renal and urinary disorders	10 (11)	8 (17)
Proteinuria†	6 (7)	2 (4)
Ketonuria†	4 (4)	1 (2)
Pollakiuria‡	2 (2)	2 (4)
Micturition urgency	1 (1)	1 (2)
Nephrolithiasis	1 (1)	1 (2)
Glycosuria	1 (1)	0
Polyuria	1 (1)	0
Urinary incontinence‡	0	1 (2)
Urine odor abnormal‡	0	1 (2)

Metabolism and nutrition disorders	10 (11)	4 (8)
Decreased appetite†	7 (8)	2 (4)
Gout	1 (1)	1 (2)
Dehydration‡	0	1 (2)
Hyperglycemia	1 (1)	0
Hypochloremia	1 (1)	0
Hypoglycemia‡	0	1 (2)
Increased appetite‡	0	1 (2)
Malnutrition	1 (1)	0
Vascular disorders	7 (8)	4 (8)
Hypotension‡	2 (2)	2 (4)
Deep vein thrombosis‡	1 (1)	2 (4)
Hot flush†	2 (2)	0
Flushing	1 (1)	0
Hypertension	1 (1)	0
Cardiac disorders	7 (8)	0
Atrial fibrillation†	2 (2)	0
Palpitations†	2 (2)	0
Atrioventricular block first degree	1 (1)	0
Bundle branch block left	1 (1)	0
Pulseless electrical activity	1 (1)	0
Tachycardia	1 (1)	0
Blood and lymphatic system disorders	4 (4)	2 (4)
Macrocytosis‡	1 (1)	2 (4)
Leukocytosis	1 (1)	1 (2)
White blood cell disorder†	2 (2)	0
Leukopenia	1 (1)	0
Neutrophilia‡	0	1 (2)
Eye disorders	5 (6)	1 (2)
Blepharospasm	1 (1)	0
Dry eye	1 (1)	0
Eye discharge	1 (1)	0
Eye irritation	1 (1)	0
Miosis‡	0	1 (2)
Vision blurred	1 (1)	0
Visual impairment	1 (1)	0
Reproductive system and breast disorders	2 (2)	2 (4)
Benign prostatic hyperplasia	1 (1)	1 (2)
Menorrhagia‡	0	1 (2)
Menstruation irregular	1 (1)	0
Product issues	1 (1)	1 (2)
Device dislocation	1 (1)	1 (2)
Surgical and medical procedures	1 (1)	1 (2)
Central venous catheterization‡	0	1 (2)
Dental operation	1 (1)	0
Ear and labyrinth disorders	0	1 (2)
Vertigo‡	0	1 (2)
Hepatobiliary disorders	1 (1)	0
Biliary colic	1 (1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (1)	0
Seborrheic keratosis	1 (1)	0

*The safety population included all participants who received at least 1 dose of trial drug.
†Occurred with a ≥2% frequency in the sodium phenylbutyrate–taurursodiol group versus the placebo group.
‡Occurred with a ≥2% frequency in the placebo group versus the sodium phenylbutyrate–taurursodiol group.

Table S5. Summary of Treatment-Emergent Electrocardiogram Findings

Electrocardiograms collected at baseline and repeated at weeks 12 and 24 detected treatment-emergent electrocardiogram findings in three (6%) participants in the placebo group and seven (8%) participants in the sodium phenylbutyrate–taurursodiol group.

Participant	Randomization	Treatment-Emergent ECG by Central Read
Participant 1	Placebo	Flat T-wave at week 24
Participant 2	Placebo	Flat T-wave at week 24
Participant 3	Placebo	Sinus tachycardia at week 12
Participant 4	Sodium phenylbutyrate–taurursodiol	Left anterior hemiblock + sinus tachycardia at weeks 12 and 24
Participant 5	Sodium phenylbutyrate–taurursodiol	Inverted T-wave at week 12, flat T-wave at week 24
Participant 6	Sodium phenylbutyrate–taurursodiol	Inverted T-wave at early discontinuation
Participant 7	Sodium phenylbutyrate–taurursodiol	Left anterior hemiblock + flat T-wave at week 12
Participant 8	Sodium phenylbutyrate–taurursodiol	Left bundle branch block at week 24
Participant 9	Sodium phenylbutyrate–taurursodiol	Flat T-wave at week 12
Participant 10	Sodium phenylbutyrate–taurursodiol	Left anterior hemiblock weeks 12 and 24

Table S6. Estimates of Treatment Assignment on Exit Questionnaire

Questionnaire Response — no. (%)	Investigator Responses Assigned Treatment		Participant Responses Assigned Treatment	
	Active (n=89)	Placebo (n=48)	Active (n=89)	Placebo (n=48)
Missing	11 (12.4)	8 (16.7)	9 (10.1)	7 (14.6)
Active	44 (49.4)	21 (43.8)	39 (43.8)	11 (22.9)
Placebo	34 (38.2)	19 (39.6)	41 (46.1)	30 (62.5)

Table S7. Primary Reasons for Exit Questionnaire Responses

Questionnaire Response — no. (%)	Assigned Treatment		Primary Reason for Estimated Treatment Allocation
	Active (n=89)	Placebo (n=48)	
Investigators			
Active	10 (11.2)	3 (6.3)	Adverse effects of trial medication
	3 (3.4)	0	Appearance, taste, odor, or other physical characteristic of trial medication
	2 (2.2)	0	Improvement in symptoms of disease under study
	0 (0)	1 (2.1)	Other reasons
	29 (32.6)	17 (35.4)	Missing*
Placebo	3 (3.4)	1 (2.1)	Lack of adverse effects of trial medication
	2 (2.2)	2 (4.2)	Lack of improvement in symptoms of disease under study
	29 (32.6)	16 (33.3)	Missing*
Participants			
Active	12 (13.5)	1 (2.1)	Adverse effects of trial medication
	7 (7.9)	1 (2.1)	Improvement in symptoms of disease under study
	4 (4.5)	3 (6.3)	Other reasons
	4 (4.5)	0 (0)	Appearance, taste, odor, or other physical characteristic of trial medication
	12 (13.5)	6 (12.5)	Missing*
Placebo	20 (22.5)	14 (29.2)	Lack of improvement in symptoms of disease under study
	2 (2.2)	1 (2.1)	Lack of adverse effects of trial medication
	0 (0)	2 (4.2)	Appearance, taste, odor, or other physical characteristic of trial medication
	0 (0)	1 (2.1)	Improvement in symptoms of disease under study
	0 (0)	1 (2.1)	Other reasons
	19 (21.3)	11 (22.9)	Missing*

*Includes respondents who did not answer and who were not asked this question because they were not at least somewhat confident in their guess.

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8. Abbreviations List

ALS	Amyotrophic lateral sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale Revised
ATLIS	Accurate Test of Limb Isometric Strength
CBC	Complete blood count
CI	Confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
ITT	Intent-to-treat
LS	Least squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
mITT	Modified intent-to-treat
MNAR	Missing not at random
MR-PET	Magnetic Resonance-Positron Emission Tomography
NEALS	Northeast ALS Consortium
OLE	Open-label extension
PK	Pharmacokinetic
SOC	System organ class
SVC	Slow vital capacity
TSPO	Translocator protein
WOCBP	Women of childbearing potential