ORIGINAL ARTICLE

# Trial of Sodium Phenylbutyrate–Taurursodiol for Amyotrophic Lateral Sclerosis

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## ABSTRACT

### BACKGROUND

Sodium phenylbutyrate and taurursodiol have been found to reduce neuronal death in experimental models. The efficacy and safety of a combination of the two compounds in persons with amyotrophic lateral sclerosis (ALS) are not known.

### METHODS

In this multicenter, randomized, double-blind trial, we enrolled participants with definite ALS who had had an onset of symptoms within the previous 18 months. Participants were randomly assigned in a 2:1 ratio to receive sodium phenylbutyrate–taurursodiol (3 g of sodium phenylbutyrate and 1 g of taurursodiol, administered once a day for 3 weeks and then twice a day) or placebo. The primary outcome was the rate of decline in the total score on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R; range, 0 to 48, with higher scores indicating better function) through 24 weeks. Secondary outcomes were the rates of decline in isometric muscle strength, plasma phosphorylated axonal neurofilament H subunit levels, and the slow vital capacity; the time to death, tracheostomy, or permanent ventilation; and the time to death, tracheostomy, permanent ventilation, or hospitalization.

### RESULTS

A total of 177 persons with ALS were screened for eligibility, and 137 were randomly assigned to receive sodium phenylbutyrate–taurursodiol (89 participants) or placebo (48 participants). In a modified intention-to-treat analysis, the mean rate of change in the ALSFRS-R score was –1.24 points per month with the active drug and –1.66 points per month with placebo (difference, 0.42 points per month; 95% confidence interval, 0.03 to 0.81; P=0.03). Secondary outcomes did not differ significantly between the two groups. Adverse events with the active drug were mainly gastrointestinal.

### CONCLUSIONS

Sodium phenylbutyrate–taurursodiol resulted in slower functional decline than placebo as measured by the ALSFRS-R score over a period of 24 weeks. Secondary outcomes were not significantly different between the two groups. Longer and larger trials are necessary to evaluate the efficacy and safety of sodium phenylbutyrate–taurursodiol in persons with ALS. (Funded by Amylyx Pharmaceuticals and others; CENTAUR ClinicalTrials.gov number, NCT03127514.)

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Amyotrophic lateral sclerosis (ALS) is a disorder characterized by motor neuron degeneration in the motor cortex and spinal cord that leads to progressive muscle weakness.[1-3] The median survival from symptom onset is 2 to 3 years, with respiratory failure being the predominant cause of death.[1,3] Treatment for ALS currently centers on symptom management.[4] Riluzole[5,6] and edaravone[7] have been shown to modulate the course of ALS and are approved by the Food and Drug Administration (FDA).

Oral, fixed-dose coformulation of the compounds sodium phenylbutyrate and taurursodiol (also known as tauroursodeoxycholic acid) was designed to reduce neuronal death in persons with ALS by simultaneously mitigating endoplasmic reticulum stress and mitochondrial dysfunction. (The proposed mechanism of these agents is described in Section 2.1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Sodium phenylbutyrate[8-13] and taurursodiol[14,15] have been shown to attenuate neuronal death and other pathologic features in experimental models of neurodegenerative disease, including models of ALS. Pilot clinical trials have reported safety data on sodium phenylbutyrate and on taurursodiol individually in persons with ALS.[16,17] We report the results of CENTAUR, a phase 2, randomized, placebo-controlled trial that evaluated the safety and efficacy of an oral sodium phenylbutyrate–taurursodiol coformulation in persons with ALS.

## Methods

### Trial Design and Oversight

This was a randomized, double-blind, placebo-controlled trial conducted at 25 centers of the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) in the United States from June 2017 through September 2019. The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonisation and the ethical principles of the Declaration of Helsinki. Protocol approval was provided for all trial sites by a central institutional review board (the Partners Human Research Committee).[18] All the participants provided written informed consent before screening.

The trial was designed by and conducted through the NEALS network (www.neals.org), in collaboration with Amylyx Pharmaceuticals; the latter provided the active drug and placebo and was involved in the trial design, data analysis, and manuscript development. The first and last authors were primarily responsible for writing the manuscript and making the decision to submit it for publication. Medical writing assistance was paid for by Amylyx Pharmaceuticals. Confidentiality agreements were in place between the authors and Amylyx Pharmaceuticals. Participant-level data were obtained at each trial site and sent to the Coordination Center at Massachusetts General Hospital. An independent data and safety monitoring board reviewed unblinded safety data throughout the trial. Statistical analyses were performed by Pentara, the Massachusetts General Hospital Biostatistics Center, and an independent statistical consultant. All the authors vouch for the completeness and accuracy of the data, for the full reporting of adverse events, and for the fidelity of the trial to the protocol (available at NEJM.org).

### Trial Participants

The trial enrolled adults with a diagnosis of definite ALS as determined by revised El Escorial criteria (clinical evidence of both upper and lower motor neuron signs in at least three body regions)[19] who were within 18 months after symptom onset. Additional eligibility criteria included a slow vital capacity (SVC) exceeding 60% of the predicted value for a person's age, sex, and height[20] and either no use of riluzole at trial entry or use of riluzole at a stable dose for at least 30 days before screening. After edaravone became available in August 2017, the protocol was amended to allow for the use of edaravone before and during the trial. Full inclusion and exclusion criteria are provided in the protocol.

### Trial Interventions and Procedures

Eligible participants were randomly assigned in a 2:1 ratio to receive sodium phenylbutyrate–taurursodiol (3 g of sodium phenylbutyrate and 1 g of taurursodiol per sachet) or matching placebo, orally or through a feeding tube for a planned duration of 24 weeks. (For details regarding randomization and the administration of the active drug and placebo, see Sections 3.1 and 3.2 in the Supplementary Appendix.) Sodium phenylbutyrate–taurursodiol and placebo were provided in single-use sachets as a powder to be dissolved in room-temperature water before ad-

ministration. The powders were constituted to look, dissolve, and taste the same. Participants were instructed to take one sachet per day for the first 3 weeks and two sachets per day (one in the morning and one in the evening) thereafter, if unacceptable side effects did not occur. Clinic visits or telephone contacts were conducted at baseline and every 3 weeks thereafter through week 24, with a final telephone follow-up at week 28 (Table S1 in the Supplementary Appendix). Participants who completed the randomized, double-blind trial were eligible for enrollment in an open-label extension trial evaluating the long-term safety of sodium phenylbutyrate–taurursodiol for up to 132 weeks (ClinicalTrials.gov number, NCT03488524).

### OUTCOMES

The primary efficacy outcome was the rate (slope) of decline in the total score on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) from baseline through trial end at week 24. The ALSFRS-R consists of 12 items across four subdomains of bodily function (bulbar, fine motor, gross motor, and breathing), with each item scored on an ordinal scale from 0 (total loss of function) to 4 (no loss of function); therefore, total scores range from 0 to 48, with higher scores indicating better function.[21] The rates of decline in ALSFRS-R subdomain scores were evaluated as exploratory outcomes. Secondary efficacy outcomes in hierarchical order were the rate of decline in isometric muscle strength as measured by the Accurate Test of Limb Isometric Strength (ATLIS) device; the rate of decline in plasma levels of the phosphorylated axonal neurofilament H subunit (pNF-H), a potential biomarker of motor neuron degeneration[22]; the rate of decline in the SVC; the time to death, tracheostomy, or permanent assisted ventilation (>22 hours daily for >7 days)[23]; the time to death, tracheostomy, permanent assisted ventilation, or any hospitalization; the pharmacokinetics of sodium phenylbutyrate and taurursodiol; and 18-kD translocator protein (TSPO) uptake on magnetic resonance–positron emission tomography (subtrial only). Pharmacokinetic data and data on TSPO uptake are not presented here because they are still undergoing analysis.

The isometric muscle strength of six upper-limb and six lower-limb muscle groups was assessed with the ATLIS device, with at least two trials for each muscle group. Raw values were standardized to the percentage of the predicted normal strength on the basis of sex, age, weight, and height.[24] Standardized scores for the highest recorded force for each muscle group were averaged to yield total, upper-limb, and lower-limb summary scores. Plasma pNF-H analysis was conducted by Iron Horse Diagnostics with the use of an electrochemiluminescence assay previously validated in its laboratory.[25,26] Because degeneration of neurons releases pNF-H into the cerebrospinal fluid and subsequently the blood, elevated plasma levels are presumed to correlate with neuronal injury.[22,25]

Respiratory muscle function was assessed according to the SVC, measured in an upright position for at least three trials per assessment or for up to five trials when the highest and second highest of the first three measurements differed by 10% or more. SVC volumes were standardized to the percentage of the predicted normal value on the basis of age, sex, and height.[20] The highest recorded SVC score from all attempts was used for analysis. Additional details regarding outcome assessments are provided in Sections 3.3 and 3.4 in the Supplementary Appendix. Adherence to sodium phenylbutyrate–taurursodiol and placebo was assessed as described in Table S2. An exit questionnaire was administered at the final trial visit (week 24 or at early discontinuation) to evaluate concealment of the trial-group assignments from the participants and investigators.

Safety was assessed through documentation at each trial visit of adverse events that occurred during the treatment period. Symptoms of ALS progression, including those consistent with disease progression, were recorded as adverse events. Any worsening of a disease-progression measure that was being analyzed separately (i.e., ALSFRS-R score, ATLIS score, and SVC) was not recorded as an adverse event.

### STATISTICAL ANALYSIS

To calculate sample size, data from the first 6 months of a large ALS trial (the Ceftriaxone Study[27]) were analyzed; only data from the participants who met key inclusion criteria used in the CENTAUR trial (diagnosis of definite ALS by El Escorial criteria and within 18 months after symptom onset) were included in the analysis. A shared-baseline, mixed-effects regression model

was used, with no added covariates. This analysis showed that, with a 2:1 randomization ratio between sodium phenylbutyrate–taurursodiol and placebo, approximately 131 participants followed over a period of 6 months would provide 80% power to detect a 30% difference in the rate of decline in the ALSFRS-R total score between the sodium phenylbutyrate–taurursodiol group and the placebo group at a two-sided alpha level of 0.1. We expected that including the prebaseline ALSFRS-R slope (the rate of change in the ALSFRS-R total score from symptom onset to baseline)[28] and age as covariates in the model and increasing assessment frequency (nine assessments over a period of 6 months in the CENTAUR trial, as compared with four assessments over a period of 6 months in the Ceftriaxone Study) would add power, allowing for the use of the prespecified two-sided alpha level of 0.05.

Safety analyses were performed in the safety population, which included all the participants who received at least one dose of sodium phenylbutyrate–taurursodiol or placebo. The primary population for efficacy analyses was the modified intention-to-treat population, which included all the participants who received at least one dose of sodium phenylbutyrate–taurursodiol or placebo and had at least one ALSFRS-R total score recorded after randomization. A post hoc analysis in the intention-to-treat population, including two participants in the active-drug group who did not undergo a postbaseline efficacy assessment and were excluded from the modified intention-to-treat population, was also performed.

A hierarchical analysis plan was used to control type I error for secondary outcomes. The ATLIS total score was the first secondary outcome; 95% confidence intervals that were unadjusted for multiple comparisons are presented for the ATLIS upper-limb and lower-limb measurements as exploratory outcomes. The subsequent items in the hierarchy were the rate of change in plasma pNF-H levels; the rate of decline in the SVC; the time to death, tracheostomy, or permanent ventilation; and the time to death, tracheostomy, permanent ventilation, or hospitalization. Sodium phenylbutyrate and taurursodiol pharmacokinetics were fifth in the hierarchy. After failure of statistical significance, the next items in the hierarchy are reported as point estimates and 95% confidence intervals unadjusted for multiple comparisons, without P values.

The absolute scores for all continuous efficacy outcomes were analyzed with the use of a random-slope, shared-baseline, linear mixed model adjusted for age and prebaseline ALSFRS-R slope — both of these covariates have been shown to be relevant in historical data.[29,30] Analyses to confirm the linear model are described in Section 3.5 in the Supplementary Appendix. A post hoc change-from-baseline analysis was performed with baseline score as a covariate (Fig. S1).

The time to death, tracheostomy, or permanent ventilation and the time to death, tracheostomy, permanent ventilation, or hospitalization were analyzed with the use of a Cox proportional-hazards model, with the same covariates as used in the primary model. Inferential testing was based on likelihood ratio tests.

Primary efficacy analyses used all available baseline and postbaseline data for all the participants in the modified intention-to-treat sample, including those who discontinued sodium phenylbutyrate–taurursodiol or placebo but remained in the trial. For these analyses, no imputation was performed for missing data. Sensitivity analyses were performed to evaluate the effects of missing data — as well as death, tracheostomy, or permanent ventilation and concomitant use of riluzole, edaravone, or both — on the primary analysis (see Section 3.5 in the Supplementary Appendix). Analyses were performed with the use of SAS software, version 9.4 (SAS Institute). A two-tailed P value of 0.05 or less was considered to indicate statistical significance.

## RESULTS

### TRIAL PARTICIPANTS

A total of 177 persons with ALS were screened for eligibility, of whom 137 were randomly assigned to a trial group: 89 to sodium phenylbutyrate–taurursodiol and 48 to placebo (Fig. 1). Two participants in the sodium phenylbutyrate–taurursodiol group, both of whom died soon after randomization, did not have a postbaseline efficacy assessment and were excluded from the primary analysis but were included in the safety population and in post hoc intention-to-treat analyses. In the modified intention-to-treat population, 69% of the participants in the sodium phenylbutyrate–taurursodiol group and 77% of those in the placebo group completed the trial

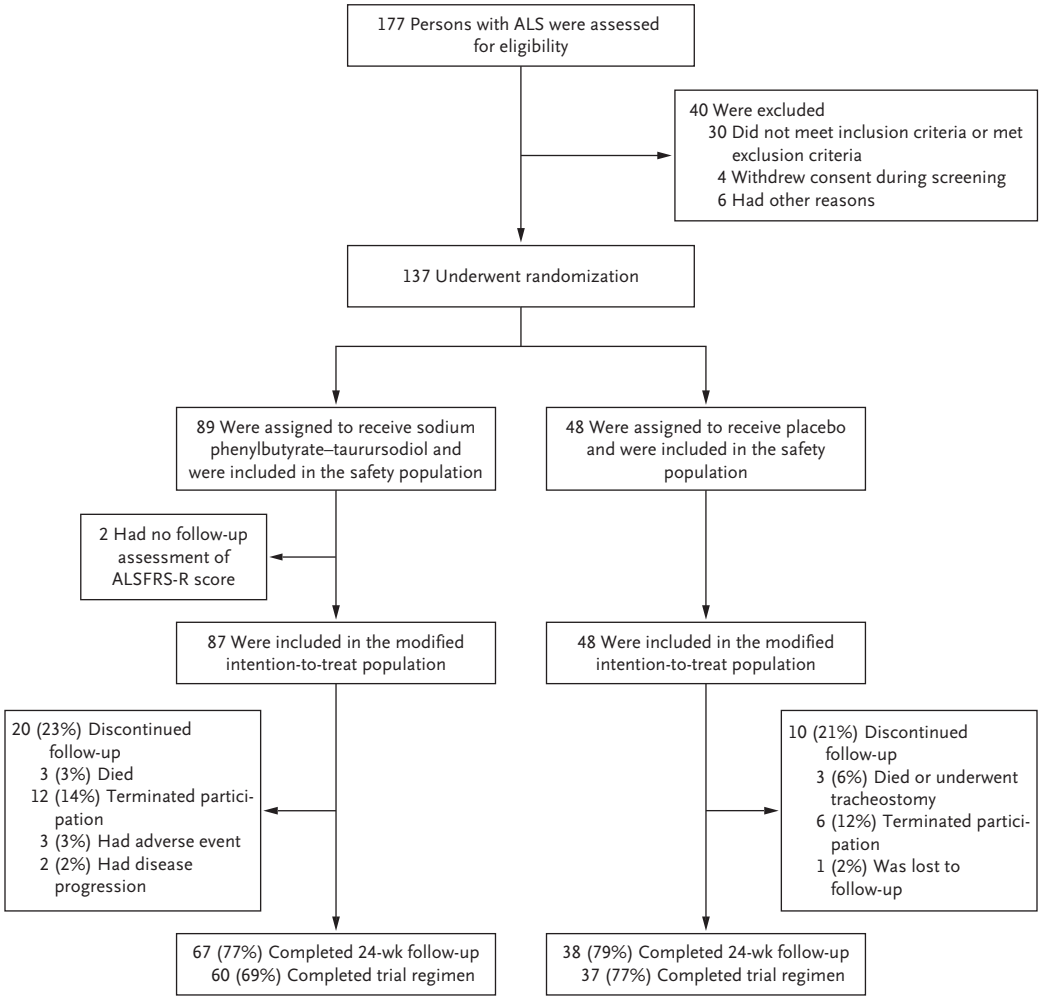


**Figure 1. Screening, Randomization, and Follow-up.**

Two participants in the sodium phenylbutyrate–taurursodiol group died before a postbaseline assessment of the score on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) could be performed, and they were excluded from the modified intention-to-treat population. One of these participants died from cardiac arrest caused by aspiration pneumonia before the week 3 visit; this participant received 18 days of therapy at a once-a-day regimen. The other participant received only five sachets of sodium phenylbutyrate–taurursodiol over a 1-month period and then discontinued treatment. This participant died approximately 1 month after discontinuing treatment subsequent to surgery for a perforated diverticulitis. ALS denotes amyotrophic lateral sclerosis.

regimen (Fig. 1). A total of 7 participants in the sodium phenylbutyrate–taurursodiol group and 1 in the placebo group who discontinued the trial regimen before the end of the trial completed the planned 24 weeks of follow-up, and the modified intention-to-treat analyses included all their available data. Because of an early error in kit distribution, the first 17 participants were assigned to the active drug and the next 9 to receive placebo; the results of a sensitivity analysis that excluded participants who were affected by this error did not differ meaningfully from the results of the primary analysis.

Baseline demographic and disease characteristics are summarized in Table 1. Most participants (77%) were receiving riluzole or edaravone at or before trial entry, with 28% of participants receiving both; a higher percentage of the participants in the placebo group (50%) were receiving edaravone at or before trial entry than in the

**Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).***

| Characteristic | Sodium Phenylbutyrate–Taurursodiol (N=87) | Placebo (N=48) | Overall (N=135) |
|---|---|---|---|
| Male sex — no. (%) | 61 (70) | 32 (67) | 93 (69) |
| White race — no. (%)† | 82 (94) | 46 (96) | 128 (95) |
| Age — yr | 57.6±10.4 | 57.3±7.6 | 57.5±9.5 |
| Bulbar onset — no. (%) | 26 (30) | 10 (21) | 36 (27) |
| Riluzole or edaravone use — no. (%)‡ | 62 (71) | 42 (88) | 104 (77) |
| Riluzole | 59 (68) | 37 (77) | 96 (71) |
| Edaravone | 22 (25) | 24 (50) | 46 (34) |
| Both | 19 (22) | 19 (40) | 38 (28) |
| Prebaseline ALSFRS-R slope§ | 0.95±0.43 | 0.93±0.60 | 0.94±0.49 |
| Slow vital capacity — % of predicted normal value | 83.6±18.2 | 83.9±15.9 | 83.7±17.4 |
| ALSFRS-R total score§ | 35.7±5.8 | 36.7±5.1 | 36.0±5.5 |
| Bulbar score | 9.5±2.4 | 10.0±2.6 | 9.7±2.5 |
| Fine-motor score | 8.0±2.7 | 8.0±2.6 | 8.0±2.7 |
| Gross-motor score | 7.5±2.8 | 7.6±2.6 | 7.6±2.8 |
| Breathing score | 10.6±1.9 | 11.0±1.8 | 10.8±1.9 |
| ATLIS upper-limb score — % of predicted normal value¶ | 54.8±24.4 | 51.4±25.2 | 53.6±24.6 |
| ATLIS lower-limb score — % of predicted normal value¶ | 57.6±24.9 | 57.1±25.8 | 57.4±25.1 |
| ATLIS total score — % of predicted normal value¶ | 56.8±20.1 | 53.9±20.9 | 55.8±20.4 |
| Months since ALS symptom onset | 13.5±3.8 | 13.6±3.6 | 13.5±3.8 |
| Months since ALS diagnosis | 5.9±3.3 | 6.3±3.2 | 6.0±3.3 |
| Body-mass index‖ | 26.9±4.4 | 26.4±5.8 | 26.7±4.9 |

* Plus–minus values are means ±SD. ALS denotes amyotrophic lateral sclerosis.
† Race was reported by the trial participant.
‡ Data are for use at or before trial entry.
§ The Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) measures 12 items in four domains of function, each scored on a scale from 0 to 4, with higher scores indicating better function.[21] The prebaseline ALSFRS-R slope was defined as the rate of decline in the total score from symptom onset to baseline.
¶ Values for the Accurate Test of Limb Isometric Strength (ATLIS) were standardized to the percentage of the predicted normal value on the basis of sex, age, weight, and height.[24]
‖ The body-mass index is the weight in kilograms divided by the square of the height in meters.

sodium phenylbutyrate–taurursodiol group (25%). A higher percentage of the participants in the sodium phenylbutyrate–taurursodiol group than in the placebo group had bulbar-onset ALS (30% vs. 21%).

### PRIMARY OUTCOME

The estimated mean rates of change of the ALSFRS-R total score in the modified intention-to-treat population were –1.24 points per month with sodium phenylbutyrate–taurursodiol and –1.66 points per month with placebo (difference, 0.42 points per month; 95% confidence interval [CI], 0.03 to 0.81; P=0.03) (Table 2 and Fig. S2). The post hoc intention-to-treat analysis, including all 137 participants who underwent randomization, yielded results that were similar to those of the modified intention-to-treat analysis (Table S3).

In a sensitivity analysis, correction for use of edaravone gave a result that was in the same direction as the results of the primary analysis but showed an estimated between-group difference in week 24 ALSFRS-R total scores of 2.15 points (95% CI, –0.05 to 4.35) (Fig. S3). A sensitivity analysis that corrected for use of riluzole yielded an estimated between-group difference

**Table 2. Efficacy Results (Modified Intention-to-Treat Population).***

| Outcome | Least-Squares Mean Change per Month† | | Least-Squares Mean at Week 24† | | | Estimated Percentage of Patients with Event | | Hazard Ratio (95% CI)‡ |
|---|---|---|---|---|---|---|---|---|
| | Sodium Phenylbutyrate–Taurursodiol (N=87) | Placebo (N=48) | Sodium Phenylbutyrate–Taurursodiol (N=87) | Placebo (N=48) | Least-Squares Difference (95% CI)†§ | Sodium Phenylbutyrate–Taurursodiol (N=87) | Placebo (N=48) | |
| **Primary outcome** | | | | | | | | |
| ALSFRS-R total score | −1.24±0.12 | −1.66±0.16 | 29.06±0.78 | 26.73±0.98 | 2.32 (0.18 to 4.47)¶ | | | |
| **Secondary outcomes: continuous** | | | | | | | | |
| ATLIS total score — % of predicted normal value‖ | −3.03±0.19 | −3.54±0.26 | 39.08±1.99 | 36.26±2.22 | 2.82 (−0.67 to 6.31) | | | |
| ATLIS upper-limb score — % of predicted normal value‖** | −3.04±0.23 | −3.81±0.31 | 36.63±2.32 | 32.36±2.59 | 4.27 (0.16 to 8.38) | | | |
| ATLIS lower-limb score — % of predicted normal value‖** | −2.98±0.24 | −3.36±0.33 | 41.17±2.37 | 39.09±2.66 | 2.09 (−2.23 to 6.41) | | | |
| Plasma pNF-H level — pg/ml | 3.58±3.19 | −2.34±4.20 | 406.95±35.82 | 374.25±38.81 | 32.70 (−24.34 to 89.75) | | | |
| Slow vital capacity — % of predicted normal value | −3.10±0.31 | −4.03±0.42 | 66.17±2.33 | 61.06±2.81 | 5.11 (−0.54 to 10.76) | | | |
| **Secondary outcomes: survival** | | | | | | | | |
| Death, tracheostomy, or hospitalization†† | | | | | | 19.3±4.2 | 33.1±6.9 | 0.53 (0.27 to 1.05) |
| Death or tracheostomy†† | | | | | | 2.8±1.7 | 4.4±3.0 | 0.63 (0.11 to 3.92) |
| Hospitalization | | | | | | 17.5±4.1 | 29.7±6.6 | 0.54 (0.27 to 1.12) |

* Plus–minus values are means, differences, or percentages ±SE. The term pNF-H denotes phosphorylated axonal neurofilament H subunit.
† Least squares denotes a mean or difference adjusted for terms in the model.
‡ The hazard ratio is for sodium phenylbutyrate–taurursodiol as compared with placebo.
§ The difference was calculated as the value in the sodium phenylbutyrate–taurursodiol group minus the value in the placebo group. Unadjusted 95% confidence intervals are shown.
¶ P=0.03; no other P values are reported, in accordance with the prespecified hierarchical order of outcomes.
‖ The numbers of participants who are represented at week 24 are as follows: 32 in the placebo group and 55 in the sodium phenylbutyrate–taurursodiol group for the ATLIS total score; 32 and 55, respectively, for the ATLIS upper-limb score; and 33 and 56, respectively, for the ATLIS lower-limb score. For the numbers of participants in each group at other time points, see Figure S5A through S5C in the Supplementary Appendix.
** These are presented as exploratory outcomes.
†† These secondary outcomes encompassed time to death, tracheostomy, permanent assisted ventilation, or hospitalization and time to death, tracheostomy, or permanent assisted ventilation (as described in the protocol). One tracheostomy occurred in the placebo group; there were no instances of permanent assisted ventilation delivered by noninvasive means.

in week 24 ALSFRS-R total scores of 2.34 points (95% CI, 0.19 to 4.48). In exploratory analyses, ALSFRS-R subdomain scores did not differ significantly between the two groups, with the exception of the fine-motor subscore (Fig. S4). Additional sensitivity and post hoc analysis results are presented in Figures S1 and S3.

### SECONDARY OUTCOMES

The mean rate of change per month in the ATLIS total score was −3.03% of the predicted normal value per month with sodium phenylbutyrate–taurursodiol and −3.54% of the predicted normal value per month with placebo (difference, 0.51 percentage points per month; 95% CI, −0.12 to 1.14) (Table 2 and Fig. S5A). As a result of the failure of hierarchical analysis at this first secondary outcome, this and subsequent secondary outcomes in the hierarchy are presented without P values. Exploratory results for the ATLIS upper-limb and lower-limb scores are shown in Table 2 and Figure S5B and S5C.

The mean rate of change in the plasma pNF-H concentration was 3.58 pg per milliliter per month with sodium phenylbutyrate–taurursodiol and −2.34 pg per milliliter per month with placebo (difference, 5.92 pg per milliliter per month; 95% CI, −4.41 to 16.26) (Table 2). The mean rate of change in the SVC was −3.10% of the predicted normal value per month and −4.03% of the predicted normal value per month in the respective groups (difference, 0.93 percentage points per month; 95% CI, −0.10 to 1.95) (Table 2 and Fig. S5D). The cumulative probability of survival free from tracheostomy or hospitalization is summarized in Figure S6; there were no instances of permanent ventilation delivered by noninvasive means. Each participant's vital status was accounted for at the end of the trial. The cumulative hazard ratio for death, tracheostomy, or hospitalization in the active-drug group, as compared with the placebo group, was 0.53 (95% CI, 0.27 to 1.05) (Table 2). Death occurred in five participants (6%) who received sodium phenylbutyrate–taurursodiol and in two participants (4%) who received placebo. Two of the deaths in the sodium phenylbutyrate–taurursodiol group were not represented in the modified intention-to-treat population. The most common cause of death was respiratory failure, accounting for four of the seven deaths, a finding consistent with the natural history of ALS. Results of post hoc secondary outcome analyses are presented in Figure S1 and Table S3.

### SAFETY

A total of 97% of the participants in the sodium phenylbutyrate–taurursodiol group and 96% of those in the placebo group had one or more adverse events during the trial (Table 3 and Table S4). Events occurring at 2% or greater frequency in the sodium phenylbutyrate–taurursodiol group were primarily gastrointestinal (diarrhea, nausea, salivary hypersecretion, and abdominal discomfort); all but salivary hypersecretion are adverse events that are known to be associated with taurursodiol. Gastrointestinal adverse events were reported more frequently in the active-drug group than in the placebo group during the first 3 weeks, with nausea, diarrhea, and abdominal pain accounting for most such events; thereafter, these events were reported less frequently in the active-drug group than in the placebo group for the remainder of the trial (Fig. S7). Dose reduction and dose interruption due to gastrointestinal events occurred more frequently in the sodium phenylbutyrate–taurursodiol group (3% and 9%, respectively) than in the placebo group (0% and 2%, respectively). Mean changes in weight from baseline to week 24 were similar in the two groups. Digital electrocardiography that was performed at baseline and repeated at weeks 12 and 24 with centralized evaluation showed asymptomatic electrocardiographic changes, including left anterior hemiblock, left bundle-branch block, and nonspecific T-wave changes in seven participants in the sodium phenylbutyrate–taurursodiol group and three participants in the placebo group (Table S5). Corrected QT intervals remained stable and did not differ significantly between the active-drug group and the placebo group at any time point.

Serious adverse events were more frequent in the placebo group than in the sodium phenylbutyrate–taurursodiol group (19% vs. 12%). The incidence of respiratory serious adverse events was 8% in the placebo group and 3% in the sodium phenylbutyrate–taurursodiol group.

A total of 19% of the participants in the sodium phenylbutyrate–taurursodiol group prematurely discontinued the trial regimen owing to adverse events, as compared with 8% in the placebo group. The most common adverse events leading to discontinuation of the trial regimen

**Table 3. Summary of Adverse Events That Occurred during the Treatment Period.***

| Variable | Sodium Phenylbutyrate–Taurursodiol (N=89) | Placebo (N=48) |
|---|---|---|
| **Adverse events** | | |
| ≥1 Adverse event — no. (%) | 86 (97) | 46 (96) |
| No. of distinct events | 618 | 328 |
| Trial regimen interrupted owing to adverse event — no. (%) | 13 (15) | 6 (12) |
| Dose reduced owing to adverse event — no. (%) | 4 (4) | 0 |
| Trial regimen discontinued owing to adverse event — no. (%) | 17 (19) | 4 (8) |
| Adverse event considered to be related to intervention | 13 (15) | 1 (2) |
| Adverse event considered to be unrelated to intervention | 4 (4) | 3 (6) |
| **Serious adverse events** | | |
| ≥1 Serious adverse event — no. (%) | 11 (12) | 9 (19) |
| No. of distinct events | 14 | 10 |
| Death — no. (%) | 5 (6) | 2 (4) |
| ≥1 Serious adverse event considered to be related to intervention — no. (%) | 1 (1) | 1 (2) |
| Trial regimen discontinued owing to serious adverse event — no. (%) | 1 (1) | 3 (6) |
| Serious adverse event considered to be related to intervention | 0 | 0 |
| Serious adverse event considered to be unrelated to intervention | 1 (1) | 3 (6) |
| **Adverse events with ≥5% incidence in either group — no. (%)†** | | |
| Gastrointestinal disorders | 60 (67) | 29 (60) |
| Musculoskeletal and connective-tissue disorders | 38 (43) | 21 (44) |
| Injury, poisoning, and procedural complications | 35 (39) | 23 (48) |
| Nervous-system disorders | 33 (37) | 19 (40) |
| Infections and infestations | 28 (31) | 21 (44) |
| Respiratory, thoracic, and mediastinal disorders | 29 (33) | 10 (21) |
| General disorders and administration-site conditions | 20 (22) | 13 (27) |
| Skin and subcutaneous-tissue disorders | 16 (18) | 8 (17) |
| Psychiatric disorders | 14 (16) | 9 (19) |
| Renal and urinary disorders | 10 (11) | 8 (17) |
| Metabolism and nutrition disorders | 10 (11) | 4 (8) |
| Cardiac disorders‡ | 7 (8) | 0 |
| Eye disorders | 5 (6) | 1 (2) |

* The safety population included all the participants who received at least one dose of sodium phenylbutyrate–taurursodiol or placebo. The relatedness of adverse events or serious adverse events to the intervention was determined by the site investigator.
† Adverse events and serious adverse events were classified according to system organ class and preferred term in the *Medical Dictionary for Regulatory Activities*, version 16.1.
‡ Adverse events were reported by the investigator and included both electrocardiographic (ECG) abnormalities and symptoms such as heart pounding and palpitations. For details on central reading of ECG abnormalities, see Table S5.

(occurring in ≥5% of the participants in either group) were diarrhea (6% in the sodium phenylbutyrate–taurursodiol and none in the placebo group) and respiratory failure (6% in the placebo group and none in the sodium phenylbutyrate–taurursodiol group).

Data on adherence to the trial regimen are summarized in Table S2. The exit questionnaire

showed no substantial evidence of unblinding of investigators or participants due to adverse events or to the taste of sodium phenylbutyrate–taurursodiol or placebo (Tables S6 and S7).

## DISCUSSION

This trial involving persons with ALS showed that treatment with coformulated, fixed-dose sodium phenylbutyrate–taurursodiol slowed the rate of decline in the ALSFRS-R total score, a measure of function in daily activities.[31] After 24 weeks, there was an estimated 2.32-point absolute difference (on a 48-point scale) in the least-squares mean ALSFRS-R total scores between the sodium phenylbutyrate–taurursodiol group and the placebo group. The score, consisting of four subdomains, showed a change that was most prominent for the fine-motor subscale and less apparent for the other subscales. Treatment with sodium phenylbutyrate–taurursodiol resulted in slowing of disease progression in a population in which many participants were receiving riluzole, edaravone, or both. However, the secondary outcomes of the rate of decline in isometric muscle strength and breathing function, change in pNF-H levels, and the time to composite events including death, tracheostomy, permanent ventilation, and hospitalization, although mostly in the same direction as the primary outcome, did not differ significantly between the two groups. In sensitivity analyses that accounted for use of edaravone and riluzole, the results were in the same direction as the results of the primary analysis, but the analysis that corrected for edaravone did not reach statistical significance.

Although both survival and functional scales are identified as suitable primary outcomes in ALS trials by the FDA[31] and the revised Airlie House consensus guidelines,[32] the use of survival as a primary outcome requires large sample sizes and a long follow-up time to achieve adequate statistical power.[23] The ALSFRS-R is the principal functional end point referenced in the latest FDA guidance for clinical trials in ALS and has been shown to correlate with survival as well as quality of life, with each point decrease representing lost capability in performing an important daily function.[21] However, there are limitations to using this measure. There is debate suggesting that the sum of ALSFRS-R subdomain scores is not a valid representation of disease severity.[33] In addition, the literature relating to what constitutes a clinically meaningful absolute change in the ALSFRS-R total score is limited. Finally, given the heterogeneity of progression in ALS, the decline in the ALSFRS-R total score may not be linear, as was assumed in our analyses; however, in our trial population that was followed for only 24 weeks, the observed change in the ALSFRS-R total score was well approximated by a linear model based on post hoc visit-by-visit estimates in the primary analysis and in an analysis including a quadratic term for time (Fig. S2 and Section 3.5 in the Supplementary Appendix, respectively).

The mean rate of change in plasma pNF-H levels did not differ significantly between the two groups over the 24-week trial duration. Although plasma sampling offers a more convenient and less invasive means of measuring pNF-H levels, cerebrospinal fluid levels have been shown to have a higher correlation with disease severity and progression in persons with ALS.[34] Newer-generation assays may provide more sensitive measurements of pNF-H levels in plasma, allowing for better assessments of these levels and ALS progression.[35,36]

Approximately 25% of the participants who received the active drug and 21% of those who received placebo discontinued the trial. Historically, the percentage of participants in ALS trials who discontinue the trial regimen is approximately 20%, and participants with more severe disease have been more likely to discontinue.[37]

In our trial, treatment of ALS with sodium phenylbutyrate–taurursodiol resulted in a slower decline in the ALSFRS-R total score over a period of 24 weeks. Between-group differences in secondary outcomes were not significant. Participants who received sodium phenylbutyrate–taurursodiol were more likely than those who received placebo to discontinue the trial regimen owing to adverse events and to have early gastrointestinal adverse events. Longer and larger trials are necessary to evaluate the efficacy and safety of sodium phenylbutyrate–taurursodiol in persons with ALS.

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## APPENDIX

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