CLINICAL RESEARCH ARTICLE

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Slowing the loss of physical function in amyotrophic lateral sclerosis with edaravone: Post hoc analysis of ALSFRS-R item scores in pivotal study MCI186-19

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[Correction added on 7 January 2022, after first online publication. ORCID IDs have been added for authors Benjamin Rix Brooks and Stephen Apple.]

Abstract

Introduction: Phase 3 study MCI186-19 demonstrated less loss of physical function with edaravone versus placebo, as measured by the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) total score. A 1-point drop in an individual ALSFRS-R item may be clinically meaningful. We assessed ALSFRS-R item score changes to identify clinical features protected by edaravone treatment.

Methods: Time-to-event analysis was used to assess the cumulative probabilities of reductions in ALSFRS-R item scores and Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) subdomain scores.

Results: Edaravone use was accompanied by: (1) delayed drop of ≥1 point in ALSFRS-R item score for four items: salivation, walking, climbing stairs, orthopnea (unadjusted), or for two items: walking, climbing stairs (after Bonferroni correction for multiple comparisons); (2) delayed score transition from 4 or 3 at baseline to ≤2 for five items: swallowing, eating motion, walking, climbing stairs, orthopnea (unadjusted), or for one item: climbing stairs (after Bonferroni correction for multiple comparisons); and (3) delayed worsening of ALSAQ-40 domain scores representing daily living/independence, eating and drinking (unadjusted).

Discussion: These post-hoc analyses identified the ALSFRS-R item scores and ALSAQ-40 domain scores that were associated with preserved gross motor function and health-related quality of life, respectively, after edaravone treatment. Limitations of post-hoc analyses should be considered when interpreting these results. We recommend that clinical trials employing the ALSFRS-R include this type of analysis as a pre-specified secondary outcome measure.

KEYWORDS
ALSFRS-R item scores, clinical trials, disease progression, functional decline, gross motor function

1 | INTRODUCTION

The ALS Functional Rating Scale - Revised (ALSFRS-R) consists of 12 question items across four domains that are affected by the disease: bulbar functions, fine motor tasks, gross motor tasks, and respiratory function.[1] Even a 1-point drop in ALSFRS-R item score in some domains is clinically meaningful for the patient.[2] In addition, some of the ALSFRS-R items, such as walking and climbing stairs, represent key functional measures for patients and can serve as surrogate assessments of treatment. On ALSFRS-R items, a score of 3 (with normal being 4) may represent a minor, but clinically defined, functional abnormality or impairment in independent performance, whereas a score of 2 typically represents a clear disturbance and/or the need for assistance. Thus, assessing the cumulative probability of patients' transitioning from a score of 4 or 3 to 2 or less on the individual items of the ALSFRS-R may reveal the potential effects of edaravone (or other treatment) on preserving physical function in ALS, and it may indicate which motor functions are primarily protected, thus sustaining the ALSFRS-R total score.

In a Phase 3, randomized, double-blind study (Study 19; MCI186-19) of edaravone in ALS patients, there was a statistically significantly slower decline in ALSFRS-R total score with edaravone compared with placebo.[3] However, how a slower decline in ALSFRS-R total score translates into clinically meaningful benefits for ALS patients remains unclear. A previous analysis of ALSFRS-R domain scores indicated that the greatest slowing of disease progression with edaravone was in the gross motor domain.[4] The objective of this study was to assess the effects of edaravone on slowing the loss of physical function in ALS, as determined by individual items on the ALSFRS-R scores, and then comparing this with ratings of patients' health-related quality of life, using the ALS Assessment Questionnaire (ALSAQ-40) scores. Based on the previous findings of the effects of edaravone treatment in ALSFRS-R domains, we hypothesized that the most notable effects estimated by the time-to-event analysis would be found in items related to the gross motor domain, that is, item 7, turning in bed and adjusting bed clothes; item 8, walking; and item 9, climbing stairs.

2 | METHODS

2.1 | Study 19 study design

Study 19 was a randomized, double-blind, parallel-group, placebo-controlled study with a 24-week double-blind period and a 24-week open-label active extension period (NCT01492686).[3,5]

The primary efficacy end point of the study was the change in ALSFRS-R total score from baseline to the end of week 24. Secondary end points included changes in (1) forced vital capacity (FVC), (2) Modified Norris Scale scores (limb, bulbar, and total), (3) ALSAQ-40 total score, (4) ALS severity classification, as well as (5) grip and pinch strength.

2.2 | Patients

Eligible consenting participants were 20 to 75 years of age, with ALS grade 1 or 2 on the Japan ALS Severity Classification; they had scores of ≥2 on all 12 items of the ALSFRS-R, a forced vital capacity (FVC) of ≥80% predicted, definite or probable ALS according to the El Escorial and revised Airlie House criteria, and duration of disease from the first symptom (any ALS symptom) of <2 years. Patients were ineligible if they had scores ≤3 on ALSFRS-R items for dyspnea, orthopnea, or respiratory insufficiency.[3]

2.3 | Post hoc statistical analyses

We conducted a post hoc analysis of Study 19 to examine the change from baseline ALSFRS-R score for the individual items of the scale during the 48 weeks of the trial. Kaplan–Meier analysis was used to conduct a time-to-event assessment where an event was defined as a drop of 1 or more points in an ALSFRS-R item score at any time during Study 19. A separate Kaplan–Meier analysis was conducted for patients who transitioned from an ALSFRS-R item score of 4 or 3 at baseline to a score of 2 or less at any time during Study 19. This measure accounts for the variable length of time to the event while using all available data for each patient. In addition, a log-rank test was used to compare the distributions of the time to an event between the: (1) edaravone and placebo group in the initial double-blind placebo-controlled portion and (2) edaravone-edaravone group and the placebo-edaravone group (where participants in this second group had a delayed start of edaravone) in the subsequent open-label extension. All result and discussion statements comparing edaravone and placebo groups are based on data derived from both portions of the 48-week study: edaravone = double-blind edaravone group plus open-label edaravone-

TABLE 1 Baseline ALSFRS-R Scores

|	Edaravone (n = 69)	Placebo (n = 68)
ALSFRS-R total and individual item mean scores (SD)		
Total mean score	41.9 (2.4)	42.8 (2.2)
1. Speech	3.4 (0.70)	3.5 (0.66)
2. Salivation	3.6 (0.67)	3.6 (0.62)
3. Swallowing	3.5 (0.72)	3.6 (0.51)
4. Handwriting	3.5 (0.58)	3.4 (0.56)
5. Eating motion	3.1 (0.84)	3.1 (0.80)
6. Dressing and hygiene	2.8 (0.68)	2.9 (0.74)
7. Turning in bed and adjusting bed clothes	3.5 (0.61)	3.4 (0.74)
8. Walking	3.3 (0.72)	3.3 (0.73)
9. Climbing stairs	2.9 (0.91)	2.9 (0.83)
10. Dyspnea	4.0 (0.0)	4.0 (0.0)
11. Orthopnea	4.0 (0.0)	4.0 (0.0)
12. Respiratory insufficiency	4.0 (0.0)	4.0 (0.0)
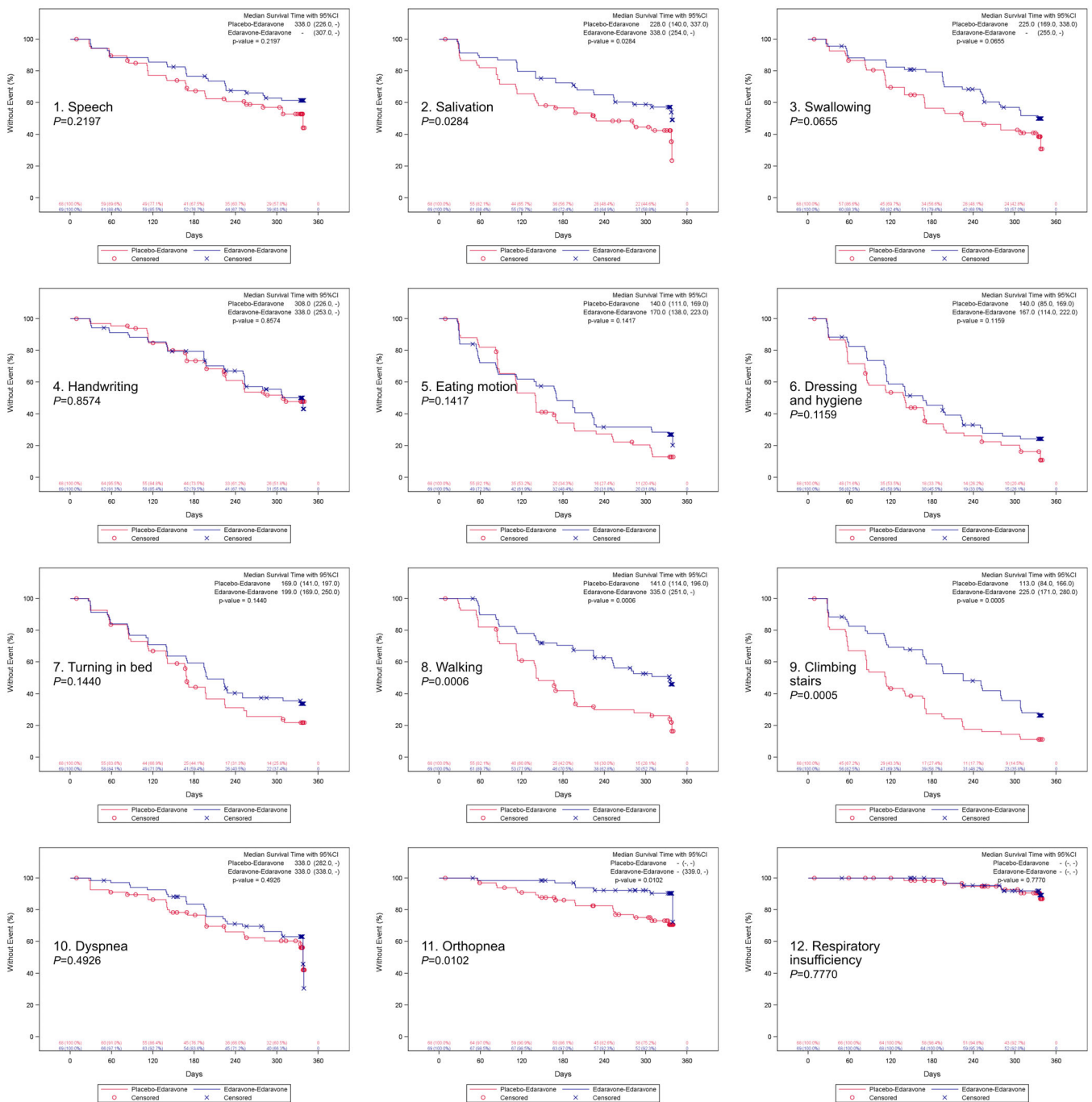
FIGURE 1 Kaplan–Meier plot of a drop of one or more points in ALSFRS-R item scores are shown for each item of the ALSFRS-R. Data from the placebo group (including the placebo-edaravone group in open-label) are shown in red lines with circles, while data from the edaravone (and edaravone-edaravone) group are shown in blue lines with × symbols

edaravone group, and placebo = double-blind placebo group plus open-label placebo-edaravone group.

Scores for the ALSAQ-40 domains that were assessed included (1) physical mobility, from questionnaire items 1 to10; (2) activities of daily living/independence, from items 11 to 20; (3) eating and drinking, from items 21 to 23; (4) communication, from items 24 to 30; and (5) emotional functioning, from items 31 to 40. An analysis of variance (ANOVA) model with a last observation carried forward (LOCF)

imputation that did not exclude any discontinuing patients was used to examine the changes from baseline to week 24 and week 48 in each of the ALSAQ-40 domains. The model included treatment group, change in ALSFRS-R score during the pre-observation period ($-3/-4$ or $-2/-1$), El Escorial revised Airlie House diagnostic criteria (definite or probable), and age (<65 or ≥65 years) as fixed effects.

The treatment differences in each parameter were evaluated both without adjustments for multiple testing and with a
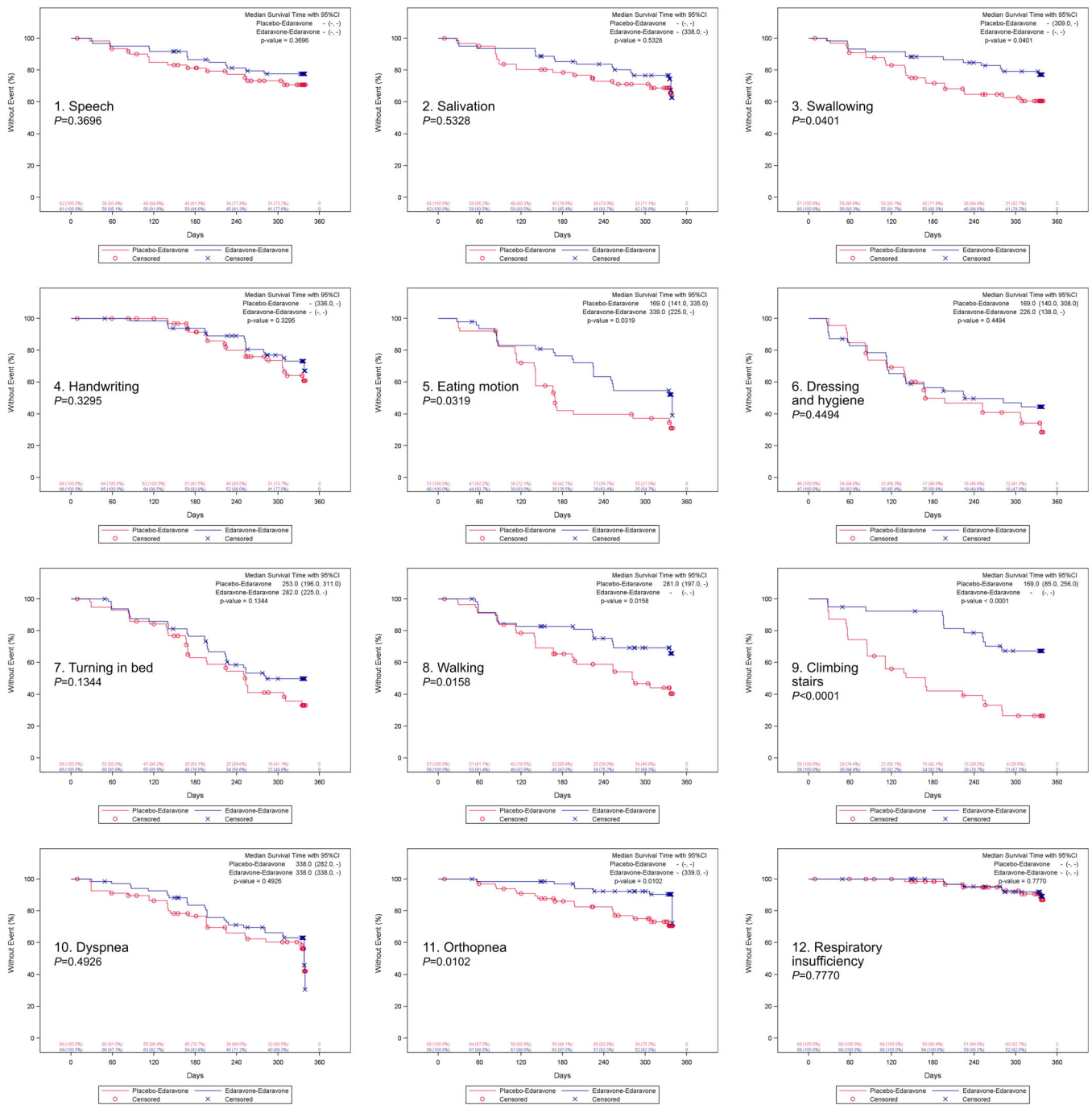
FIGURE 2   Kaplan–Meier plot of the transition of ALSFRS-R items from a score of 4 or 3 to 2 or less (respiratory is from 4 to 3 or less) are shown for each item of the ALSFRS-R. Data from the placebo group (including the placebo-edaravone group in the open-label extension) are shown in red lines with circles, while data from the edaravone (and edaravone-edaravone) group are shown in blue lines with × symbols

Bonferroni correction applied for 36 analyses. Given the statistical testing for 12 ALSFRS-R individual item scores with two types of KM analysis and six items in ALSAQ-40 total and five domain scores with Forest plots at Week 24 and Week 48, all statistical testing requires a nominal p-value of .001 to reach significance following Bonferroni correction (p = alpha/n, alpha = 0.05, n = 36).

3 | RESULTS

3.1 | Baseline characteristics

A total of 137 patients were initially randomized to receive either edaravone ($n = 69$) or placebo ($n = 68$) in the double-blind phase; 127 patients completed the clinical trial. During the double-blind phase,
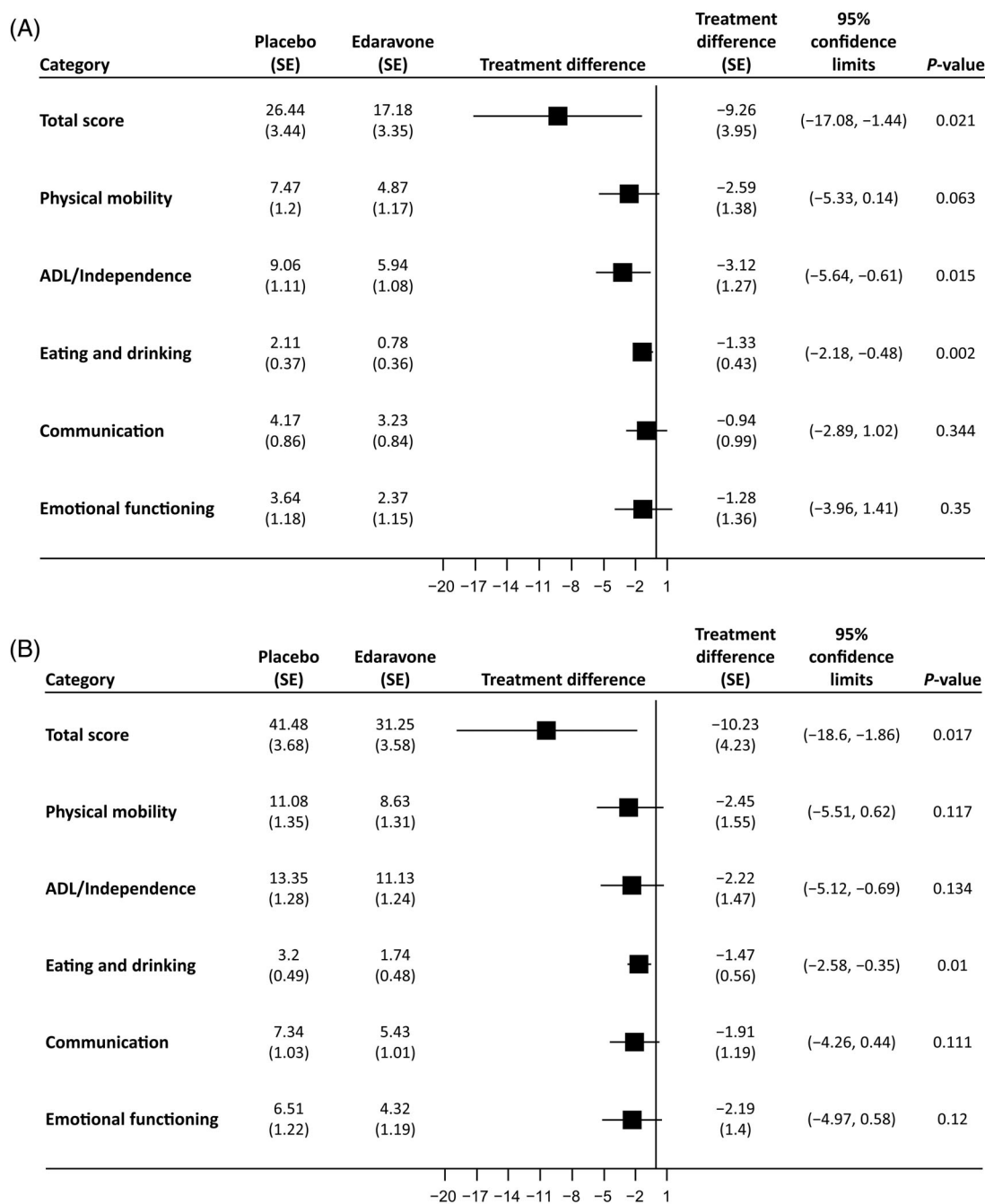
(A)

Category	Placebo (SE)	Edaravone (SE)	Treatment difference	Treatment difference (SE)	95% confidence limits	P-value
Total score	26.44 (3.44)	17.18 (3.35)		−9.26 (3.95)	(−17.08, −1.44)	0.021
Physical mobility	7.47 (1.2)	4.87 (1.17)		−2.59 (1.38)	(−5.33, 0.14)	0.063
ADL/Independence	9.06 (1.11)	5.94 (1.08)		−3.12 (1.27)	(−5.64, −0.61)	0.015
Eating and drinking	2.11 (0.37)	0.78 (0.36)		−1.33 (0.43)	(−2.18, −0.48)	0.002
Communication	4.17 (0.86)	3.23 (0.84)		−0.94 (0.99)	(−2.89, 1.02)	0.344
Emotional functioning	3.64 (1.18)	2.37 (1.15)		−1.28 (1.36)	(−3.96, 1.41)	0.35

−20 −17 −14 −11 −8 −5 −2 1

(B)

Category	Placebo (SE)	Edaravone (SE)	Treatment difference	Treatment difference (SE)	95% confidence limits	P-value
Total score	41.48 (3.68)	31.25 (3.58)		−10.23 (4.23)	(−18.6, −1.86)	0.017
Physical mobility	11.08 (1.35)	8.63 (1.31)		−2.45 (1.55)	(−5.51, 0.62)	0.117
ADL/Independence	13.35 (1.28)	11.13 (1.24)		−2.22 (1.47)	(−5.12, −0.69)	0.134
Eating and drinking	3.2 (0.49)	1.74 (0.48)		−1.47 (0.56)	(−2.58, −0.35)	0.01
Communication	7.34 (1.03)	5.43 (1.01)		−1.91 (1.19)	(−4.26, 0.44)	0.111
Emotional functioning	6.51 (1.22)	4.32 (1.19)		−2.19 (1.4)	(−4.97, 0.58)	0.12

−20 −17 −14 −11 −8 −5 −2 1

FIGURE 3 ALSAQ-40 analysis of changes from baseline to week 24 (A) and to week 48 (B) in the full analysis set (LOCF). Scores (with standard error [SE]) for the treatment arms, treatment differences, 95% confidence limits, and p-values are shown in the figure. ADL, activities of daily living

two edaravone and eight placebo patients discontinued treatment, mostly because of disease progression.[5] Of the 127 patients completing the double-blind phase, 123 patients continued into the active-treatment (open-label) period: 65 patients from the edaravone group (edaravone-edaravone) and 58 patients from the placebo group (placebo-edaravone).

Overall, the demographics and baseline characteristics of the patients were well balanced between treatment groups, except for male gender and ALS severity.[3] The mean ALSFRS-R total scores at baseline were 41.9 ± 2.4 in the edaravone arm and 41.8 ± 2.2 in the placebo arm. The individual ALSFRS-R item scores at baseline are

shown in Table 1. As required by the protocol for Study 19, the three respiratory items (dyspnea, orthopnea, and respiratory insufficiency) all had baseline mean scores of 4.

3.2 | Post hoc analyses

3.2.1 | ALSFRS-R item scores

Kaplan–Meier analysis was used to assess the time-to-event of a drop of 1 or more points for each ALSFRS-R item score. As shown in Figure 1,

delay in a drop of ≥1 point in ALSFRS-R item score was present for four items (unadjusted): 2 (salivation), 8 (walking), 9 (climbing stairs), and 11 (orthopnea), and for two items (after correction for multiple comparisons with the Bonferroni method) with statistical significance: 8 (walking, $p = .0006$) and 9 (climbing stairs, $p = .0005$). The median time to event of the edaravone group compared to the placebo group was delayed more than two-fold for items 8 (walking) and 9 (climbing stairs).

As shown in Figure 2, delay in transition of scores from 4 or 3 at baseline to ≤2 was observed for five items (unadjusted): 3 (swallowing), 5 (eating motion), 8 (walking), 9 (climbing stairs), and 11 (orthopnea), and for item 9 (climbing stairs) (after Bonferroni correction for multiple comparisons) with statistical significance ($p \leq .0001$). The median time to event of the edaravone group compared to the placebo group was delayed more than two-fold for item 9 (climbing stairs).

3.2.2 | ALSAQ-40 scores

As shown in Figure 3, ALSAQ-40 domain scores associated with slowing loss of physical function measured by ALSAQ-40 total score change accompanying edaravone use included two domains: daily living/independence, eating and drinking (unadjusted). No domains were identified as statistically significant after correction with the Bonferroni method.

4 | DISCUSSION

Edaravone treatment was associated with less functional decline compared with placebo as measured not only by ALSFRS-R total score but also in many individual ALSFRS-R item scores. The current findings of significant differences in climbing stairs and walking support our hypothesis, based on previous analyses,[4] that gross motor function is most notably affected by edaravone treatment. It is therefore an important observation that patients taking edaravone had less functional decline in lower limb ALSFRS-R items after Bonferroni correction for multiple comparisons, reflecting treatment benefit for essential functions such as walking and climbing stairs.

In this analysis, the ability to walk more independently and to climb stairs without unsteadiness or fatigue were notably prolonged with the use of edaravone.

Some items, such as handwriting and dressing and hygiene, as well as turning in bed and adjusting bed clothes, did not appear to differ significantly when the Bonferroni method was included between edaravone and placebo, whereas walking and climbing stairs remained statistically significant. When considered as a group, the different responses between items may suggest a larger comparative benefit of edaravone for lower limb function vs upper limb function, an observation that warrants further investigation.

Alternatively, the findings may also indicate something about the ALSFRS-R scale itself, where some items are more sensitive to changes than others. For example, declines in handwriting depend on which side is affected, and may be missed in patients with unilateral involvement. Other findings may fail to show changes because of the

type of patients that were selected for a trial. It may be more difficult to detect differences in respiratory function because only patients with relatively good respiratory function are enrolled in trials. Ceiling effects for these items may hinder the ability to detect declines in ALSFRS-R score during a 6- to 12-month trial. Similarly, the scale may be too sensitive for individual items that tend to change quickly in all patients. It is important to note that we found that the edaravone group resulted in fewer events on 4 ALSFRS-R items unadjusted, with statistically significant differences for walking and climbing stairs after Bonferroni correction for multiple comparisons. This is not surprising because the overall study demonstrated that this cohort had a slower rate of functional decline during the trial.

A preliminary post hoc analysis was performed to explore which domains of the ALSFRS-R score differences might identify the benefits of edaravone during the double-blind phase in Study 19.[4] Other clinical trials employing ALSFRS-R domain and item analysis have identified clinical benefits of dextromethorphan-quinidine on speech and swallowing in the ALSFRS-R bulbar domain but not in other ALSFRS-R domains in a clinical trial[6] and clinical benefits on the ALSFRS-R gross motor domain but not in other domains in a clinical trial of reldesemtiv.[7] Non-uniform or domain-specific treatment effects have been recently evaluated in a simulation analysis to assess the power requirements for sample size estimation using change from baseline or slope analyses.[8] The item specific analysis in the post hoc analysis described here employed time-to-event analysis rather than change from baseline or slope analysis in order to better understand the improvement in the information content that might be possible from clinical trials measuring function with the ALSFRS-R.

A limitation of the current study was that, unlike for the ALSFRS-R total score, the current analyses were not prespecified in Study 19 and that trial was not prospectively designed with multiplicity adjustment to control type 1 error rate in Kaplan–Meier analysis for individual items of the ALSFRS-R or the ANOVA analysis for ALSAQ-40 subdomains; however, we conducted statistical testing both with and without adjustments for multiplicity. Moreover, limitations inherent in an open-label design after week 24 and with post hoc analyses should be considered when interpreting these results.

The dextromethorphan-quinidine and the reldesemtiv clinical trials, as well as our post hoc analysis of the edaravone Study 19 clinical trial, raise issues regarding the treatment responsiveness of various items in the ALSFRS-R and how they may each contribute to overall study outcome when measured by the ALSFRS-R total score. Further studies should help explore and explain the findings described in this post hoc analysis.

5 | CONCLUSION

These analyses identify specific items of the ALSFRS-R that are preserved by edaravone treatment and contribute to a slower loss of physical functioning and health-related quality of life in patients with ALS. We recommend that future clinical trials employing the ALSFRS-R include this type of analysis as a pre-specified secondary

outcome measure because it provides information that might be useful in clinical trial interpretation and in the day-to-day management of patients and potential treatment effects.

CONFLICT OF INTEREST

BRB, EPP, and JK are consultants for MTPA. FT and KT are employees of MTPC. JZ is under contract with MTPA. SA is an employee of MTPA.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data are available on request to Mitsubishi Tanabe Pharma America, Inc, from researchers at academic institutions.

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