# A Post-hoc Analysis of Edaravone Study 19: Forced Vital Capacity (FVC) Subgroup Analysis

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## BACKGROUND

- Amyotrophic lateral sclerosis (ALS) is a progressive and debilitating neurodegenerative disease in which degeneration of motor neurons leads to muscle atrophy, paralysis, and death[1]
- Currently, there is no cure for ALS. Current treatments are available to help control symptoms and complications[1,2]
- Radicava® (edaravone) was approved by the FDA for the treatment of ALS and has been shown to slow the rate of functional decline[3]
- FDA approval was based in part on the outcomes from edaravone Study 19 (MCI-186-19), which was a randomized, double-blind, placebo-controlled study in subjects with ALS[4]
- Study 19 employed a strategic study design in order to measure a treatment effect in a 6-month timeframe utilizing the ALS Functional Rating Scale-Revised (ALSFRS-R)[5,6]
- Whether the results are generalizable to real-world utility has been questioned by both clinicians and payors[7]
  - One of the Study 19 inclusion criteria was subjects with a forced vital capacity (FVC) ≥80%, therefore questions arise regarding efficacy in patients with FVC <80%
- To address this concern, a post-hoc analysis was conducted to evaluate the effect of edaravone in subgroups differentiated by their FVC values at week 24 (FVC ≥80% vs FVC <80%)

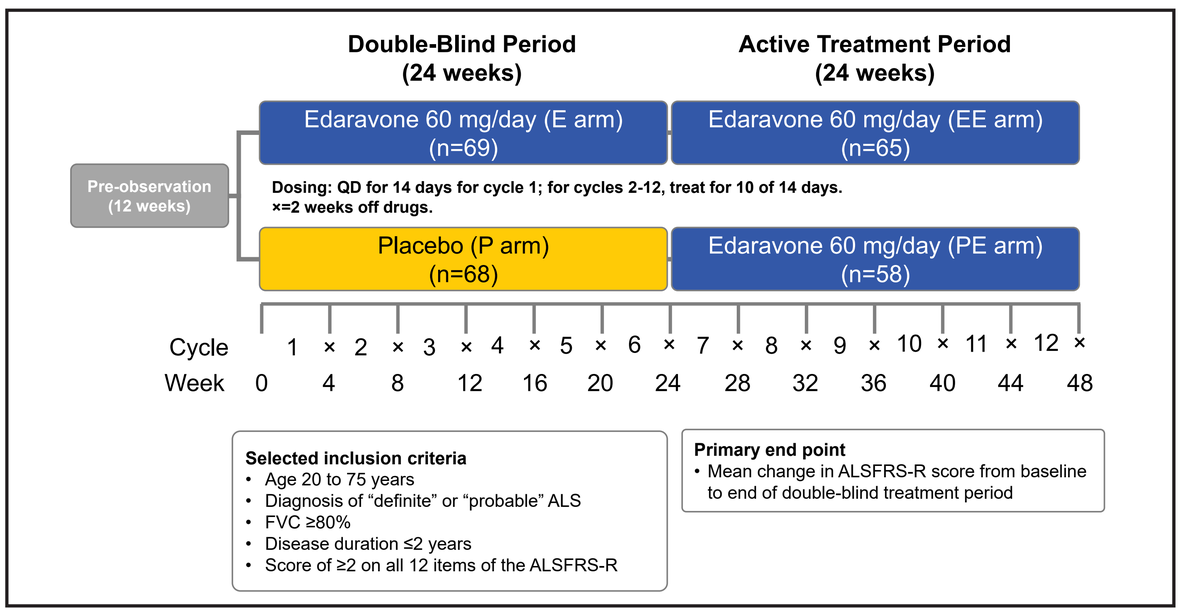
## OBJECTIVE

- To investigate the efficacy of edaravone over 24 and 48 weeks of treatment, as measured by ALSFRS-R, in patients who maintained FVC ≥80% through week 24, as compared with patients whose FVC was <80% at week 24

## METHODS

- Study 19 (MCI-186-19) was a Phase 3, randomized, double-blind, parallel-group study **(Figure 1)**
  - The study consisted of a 24-week, double-blind, placebo-controlled treatment period (cycles 1-6), followed by a 24-week, uncontrolled, open-label, active treatment period (cycles 7-12)
- FVC ≥80% and FVC <80% subgroups
  - A post-hoc analysis was conducted to examine the change from baseline ALSFRS-R at week 24 and week 48, with subjects divided into subgroups based on their FVC values at week 24 (FVC ≥80% and FVC <80%)

**Figure 1. Study design**




## RESULTS

- Study 19 included 69 subjects in the edaravone arm and 68 subjects in the placebo arm. Baseline characteristics were well balanced between treatment groups **(Table 1)**
- The mean FVC at baseline was 100.5% ± 14.97% in the edaravone arm and 97.3% ± 13.59% in the placebo arm **(Table 2)**
- For the post-hoc analysis, each arm was divided into 2 subgroups based on FVC at week 24 (end of cycle 6)
- As expected, the mean FVC values were lower in the FVC <80% subgroups than in the FVC ≥80% subgroups **(Table 2)**
  - In particular, the mean FVC was 60.3% ± 12.89% in the placebo FVC <80% subgroup
- 61.5% (40/65) of edaravone patients and 55.2% (32/58) of placebo patients maintained FVC ≥80% by week 24 **(Table 2)**

**Table 1. Baseline demographics and clinical characteristics (FAS)**

| | Edaravone (n=69) | Placebo (n=68) |
|---|---|---|
| **Gender, n (%)** | | |
| Men | 38 (55) | 41 (60) |
| Women | 31 (45) | 27 (40) |
| **Mean age (SD), yr** | 60.5 (10) | 60.1 (10) |
| **Mean duration of disease (SD), yr** | 1.13 (0.5) | 1.06 (0.5) |
| **Initial symptom, n (%)** | | |
| Bulbar symptom | 16 (23) | 14 (21) |
| Limb symptom | 53 (77) | 54 (79) |
| **ALS diagnostic criteria, n (%)[a]** | | |
| Definite | 28 (41) | 27 (40) |
| Probable | 41 (59) | 41 (60) |
| **ALS severity, n (%)[b]** | | |
| Grade 1 | 22 (32) | 16 (24) |
| Grade 2 | 47 (68) | 52 (76) |
| **Mean ALSFRS-R score (SD)** | | |
| Before observation period | 43.6 (2.2) | 43.5 (2.2) |
| Baseline (end of 12 weeks observation) | 41.9 (2.4) | 41.8 (2.2) |
| **Concomitant riluzole, n (%)** | 63 (91) | 62 (91) |

[a]According to revised El Escorial criteria.
[b]According to Japan ALS severity classification (grade 1-5, with grade 5 being most severe).
FAS=full analysis set; SD=standard deviation.

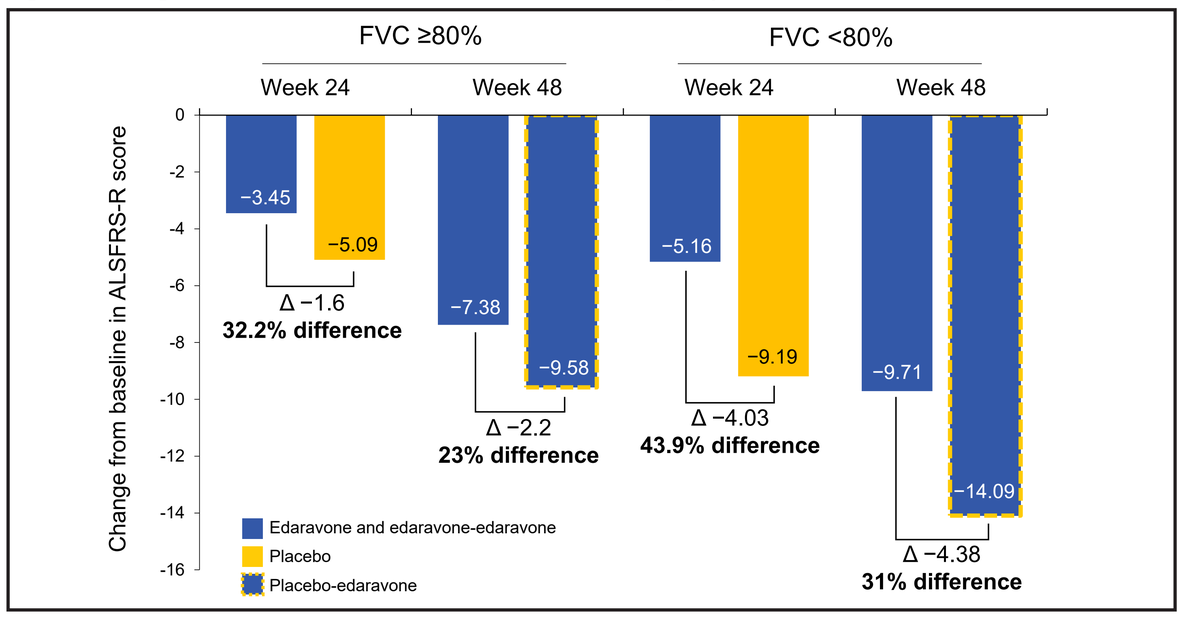
**Table 2. FVC values in the analysis subgroups**

| Group | Edaravone | Placebo |
|---|---|---|
| **Baseline** | | |
| FAS | | |
| n | 69 | 68 |
| FVC, mean (SD) | 100.5% (14.97%) | 97.3% (13.59%) |
| **Week 24 (end of cycle 6)** | | |
| FVC ≥80%[a] | | |
| n | 40 | 32 |
| FVC, mean (SD) | 103.7% (16.30%) | 97.4% (12.53%) |
| FVC <80%[b] | | |
| n | 25 | 26 |
| FVC, mean (SD) | 66.1% (8.38%) | 60.3% (12.89%) |

[a]Subgroup with FVC ≥80% at week 24 (end of cycle 6).
[b]Subgroup with FVC <80% at week 24 (end of cycle 6).

- For each FVC subgroup, the changes from baseline in ALSFRS-R scores are shown in **Figure 2**
- For FVC ≥80%
  - At week 24 (end of cycle 6): –3.45 (edaravone) vs –5.09 (placebo); a 32.2% difference
  - At week 48 (end of cycle 12): –7.38 (edaravone-edaravone) vs –9.58 (placebo-edaravone) group; a 23% difference
- For FVC <80%
  - At week 24 (end of cycle 6): –5.16 (edaravone) vs –9.19 (placebo); a 43.9% difference
  - At week 48 (end of cycle 12): –9.71 (edaravone-edaravone) vs –14.09 (placebo-edaravone); a 31% difference

**Figure 2. Change in ALSFRS-R scores from baseline in FVC subgroups at week 24 and week 48**




- Linear regression analyses were performed with the data from each FVC subgroup in each phase of the study **(Figures 3 and 4)**
- The placebo subjects from the FVC <80% subgroup demonstrated a notable change in slope in ALSFRS-R after starting edaravone therapy at week 24 **(Figure 4)**
  - The change from baseline in ALSFRS-R at week 48 for the placebo-edaravone subjects was –14.09, as compared with a projected value of –17.19 if the subjects had remained on placebo, based on linear regression of the placebo arm; a difference of 18%

**Figure 3. FVC ≥80% subgroup regression analysis**

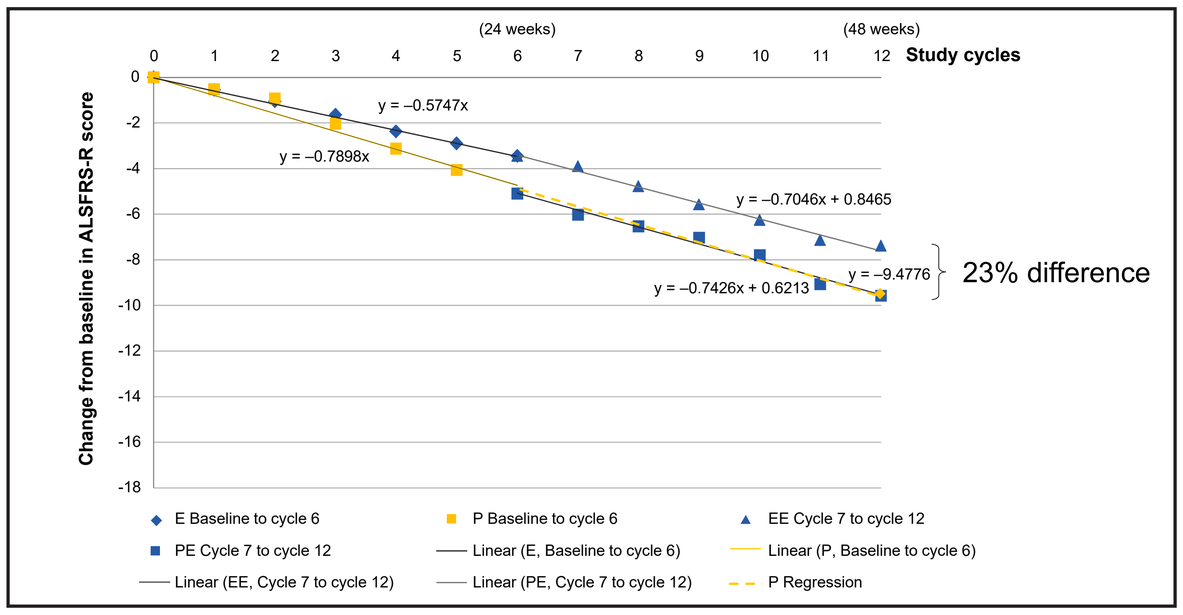
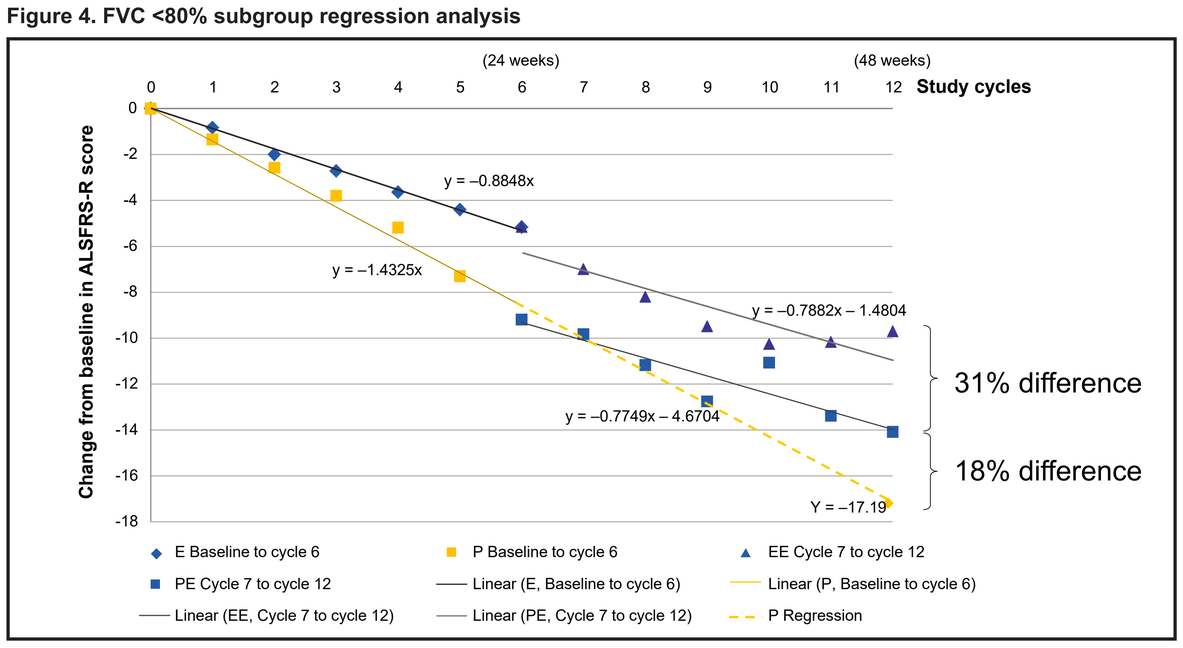



**Figure 4. FVC <80% subgroup regression analysis**




## CONCLUSIONS

- Subjects in both the FVC ≥80% and FVC <80% subgroups experienced less of a decline in ALSFRS-R score with edaravone vs placebo through week 24
- Subjects in the FVC <80% placebo subgroup (mean FVC = 60.3%) responded to edaravone treatment as demonstrated by a change in slope of the ALSFRS-R score vs time graph after starting edaravone treatment (placebo-edaravone arm)
- Overall, greater treatment effects were seen in the subgroup with FVC <80% than in that with FVC ≥80%
- This analysis suggests that edaravone has benefit in ALS patients, irrespective of whether they start treatment when their FVC is ≥80% or <80%

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