Post Hoc Analysis of Edaravone Study 19: Efficacy in Bulbar-Onset ALS Patients With and Without Reduced Pulmonary Function

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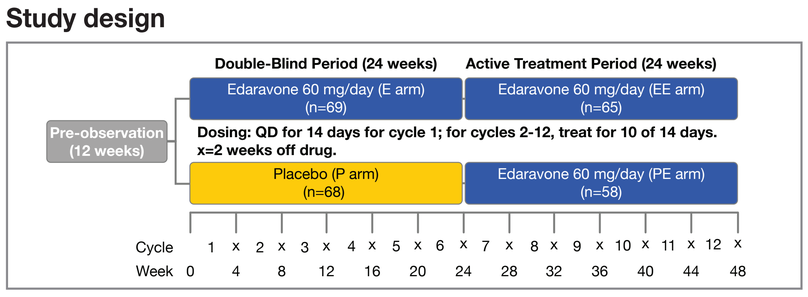
BACKGROUND

- Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neuromuscular disease, with most patients succumbing to respiratory failure[1-3]
- ALS typically begins in the limbs, but about one third of cases are bulbar, characterized by difficulty chewing, speaking, or swallowing[1]
- Bulbar dysfunction in ALS has a significant impact on quality of life and is currently the focus of the development of best practice guidelines[4]

Edaravone Study 19 Overview

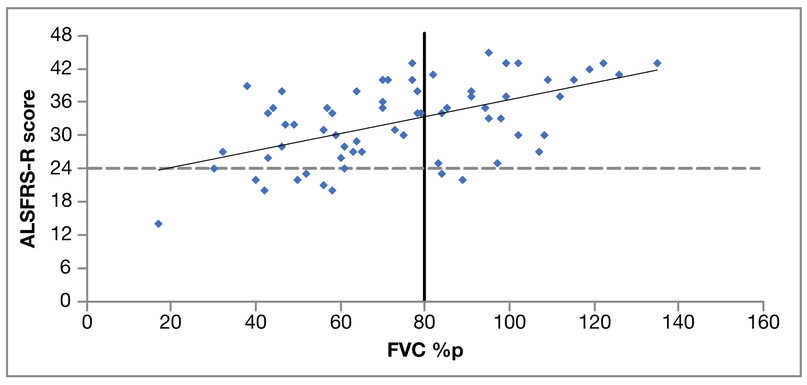
- Edaravone study MCI186-19 (Study 19) was a Phase 3, randomized, double-blind, parallel-group study[5]
  - The study consisted of a 24-week (cycles 1-6) double-blind, placebo-controlled treatment period, followed by a 24-week (cycles 7-12) uncontrolled, open-label, active treatment extension period
- As the 24-week study extension was uncontrolled, multiple linear regression analysis was used to develop a model to project the placebo arm through week 48 (cycle 12) to assess the possible long-term efficacy and safety of edaravone

Study design



- In Study 19, patients with ALS experienced significantly less functional decline with edaravone vs placebo, as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R)[5]
  - Difference between groups in change from baseline in ALSFRS-R score = 2.49 (33% difference; *P*=.0013)
- Post-hoc analysis of the ALSFRS-R score vs forced vital capacity (FVC) at week 48[6]
  - Most patients had ALSFRS-R scores >24, including those with FVC <80%
  - Thus, these patients appeared to have functionality in other domains of the ALSFRS-R that would benefit from a treatment that slows the loss of physical function

ALSFRS-R score vs FVC at week 48[6]



Each symbol represents one patient in Study 19

- A previous post hoc analysis of Study 19 seemed to reveal that ALS patients with reduced FVC of <80% prior to starting open-label edaravone received a significant benefit after initiating treatment (33% difference, *P*=.006; n=25)[6,7]
  - This study included both limb- and bulbar-onset patients; therefore, it was thought to be important to compare these groups regarding their response to edaravone treatment, and to assess bulbar patients with FVC ≥80% vs <80% at the time of treatment initiation

OBJECTIVE

- To address the efficacy of edaravone in patients with bulbar-onset ALS and bulbar patients with FVC of either ≥80% or <80%

METHODS

Post Hoc Analysis

- A post hoc analysis of Study 19 was conducted to examine the change from baseline ALSFRS-R at week 24 and week 48, with subjects divided into subgroups based on bulbar- vs limb-onset disease[a]
- Multiple linear regression analyses
  - Multiple linear regression analyses were performed to estimate the slopes of the scores for the treatment arms for the edaravone, placebo, edaravone-edaravone, and placebo-edaravone patients in each subgroup
- Analysis of disease progression in bulbar patients with FVC ≥80% vs <80%
  - Study 19 subjects were divided into subgroups based on their FVC values at week 24 (end of cycle 6: FVC <80% and FVC ≥80%)
  - The change from baseline ALSFRS-R at week 24 and week 48 was analyzed in the 2 subgroups of patients
- As a post hoc, subgroup analysis of Study 19, this study is subject to the limitations inherent in post hoc analyses (eg, analyses were not prespecified in Study 19, smaller sample sizes in each subgroup, lack of control for type 1 error)

[a]Bulbar-onset patients were identified based on whether the patient's initial symptoms were bulbar symptoms or limb symptoms, which was determined by study investigators when they enrolled patients in Study 19.
[b]ANOVA, LOCF analysis.
[c]These effects were not statistically significant, likely due to the small number of patients in the analysis.

RESULTS

Baseline Characteristics of the Analysis Populations

- The bulbar- and limb-onset patient populations were comparable at baseline in terms of age, duration of disease, and ALSFRS-R score
- Bulbar-onset patients had a higher proportion of women and may have had more severe disease than limb-onset patients

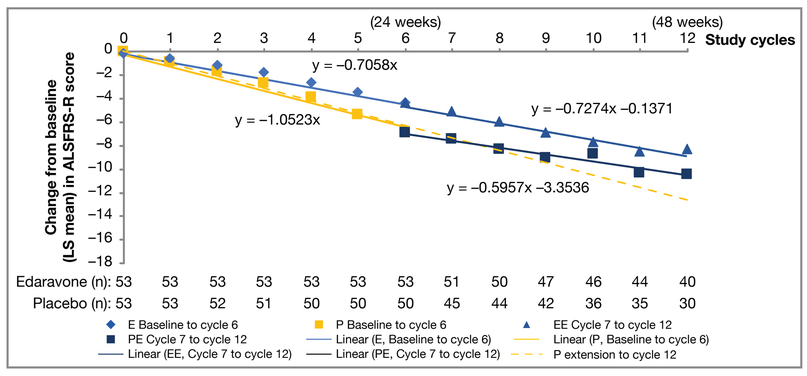
Table 1. Baseline characteristics of analysis populations

	Limb (n=107)	Bulbar (n=30)	*P* value
Gender, n (%)			
Men	68 (64)	11 (37)	.0084
Women	39 (36)	19 (63)	
Age, mean (SD)	59.6 (10)	62.7 (8)	.1229
Duration of disease, mean, years (SD)	1.10 (0.5)	1.08 (0.4)	.7859
ALS diagnostic criteria, n (%)			
Definite	39 (36)	16 (53)	.0955
Probable	68 (64)	14 (47)	
ALS severity, n (%)			
Grade 1	25 (23)	13 (43)	.0955
Grade 2	82 (77)	17 (57)	
ALSFRS-R score, mean (SD)			
Before preregistration	43.4 (2.2)	44.0 (2.1)	.2464
Baseline in cycle 1	41.8 (2.4)	42.0 (2.1)	.5824

ALSFRS-R in Study 19 Limb-Onset Patients

- In limb-onset patients, during the double-blind period, edaravone was associated with slower disease progression
  - Edaravone: –5.11
  - Placebo: –7.42

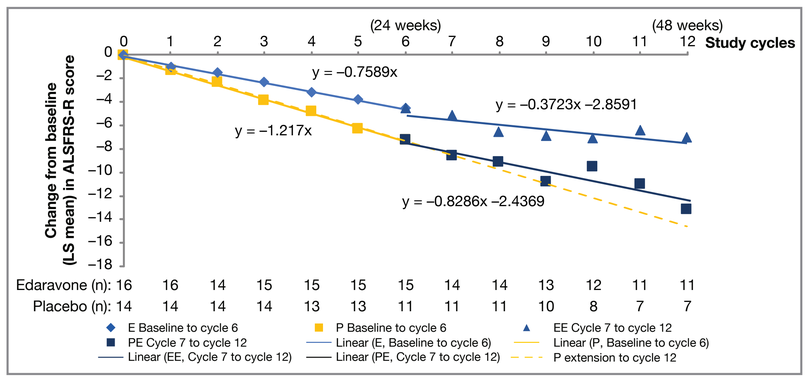
  Δ 2.31 — **31% difference** ***P*=.0103**[b]
- Placebo patients who switched to edaravone treatment after week 24 experienced a significant change in slope in ALSFRS-R score decline (*P*<.001)



ALSFRS-R in Study 19 Bulbar-Onset Patients

- In bulbar-onset patients, during the double-blind period, edaravone was associated with slower disease progression
  - Edaravone: –4.98
  - Placebo: –7.40

  Δ 2.42 — **33% difference** ***P*=.0961**[b]
- Placebo patients who switched to edaravone treatment after week 24 may have experienced a change in slope in ALSFRS-R score decline[c]



Baseline Characteristics of Bulbar Patients With FVC <80% vs ≥80% at Week 24

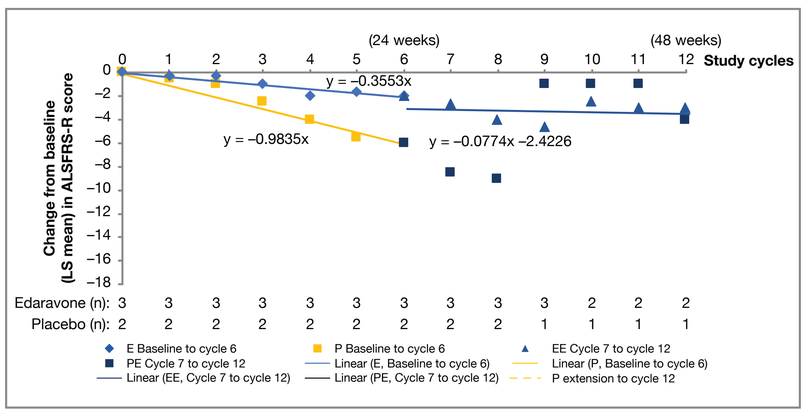
- Bulbar-onset patients were divided into 2 groups based on having FVC <80% vs ≥80% at the end of the double-blind period (cycle 6)
- At the end of the double-blind period, there were more bulbar patients with FVC <80% vs ≥80%
- The baseline characteristics of the 2 groups were comparable, although patients with FVC <80% may have had more severe disease

Table 2. Baseline characteristics for FVC ≥80% vs <80%

	FVC <80% (n=21)	FVC ≥80% (n=5)	*P* value
Gender, n (%)			
Men	6 (29)	4 (80)	.0336
Women	15 (71)	1 (20)	
Age, mean (SD)	63.6 (7)	58.2 (12)	.1782
Duration of disease, mean, years (SD)	1.07 (0.4)	1.18 (0.4)	.5751
ALS diagnostic criteria, n (%)			
Definite	10 (48)	4 (80)	.1918
Probable	11 (52)	1 (20)	
ALS severity, n (%)			
Grade 1	8 (38)	4 (80)	.1918
Grade 2	13 (62)	1 (20)	
ALSFRS-R score, mean (SD)			
Before preregistration	43.7 (2.2)	44.2 (2.2)	.6235
Baseline in cycle 1	41.6 (2.0)	42.6 (2.3)	.3534

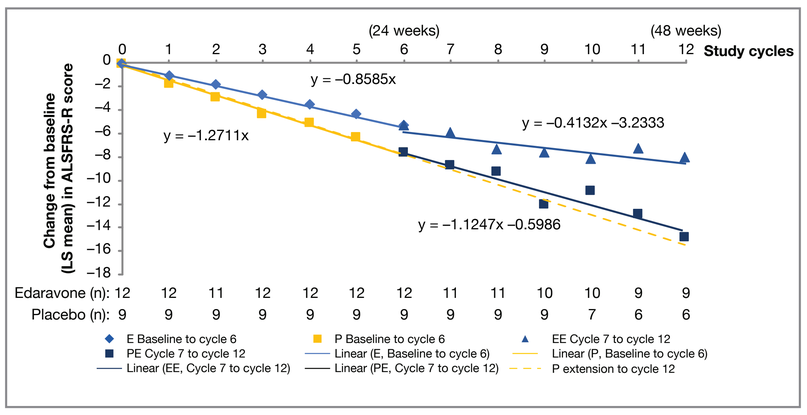
ALSFRS-R in Bulbar Patients With FVC ≥80% at Week 24

- There were very few bulbar-onset patients who maintained FVC ≥80% during the double-blind period



ALSFRS-R in Bulbar Patients With FVC <80% at Week 24

- In bulbar-onset patients who had FVC <80% at the end of the double-blind period (cycle 6):
  - Edaravone appeared to slow disease progression during the double-blind period[c]



CONCLUSIONS

- A previous post hoc analysis of the full Study 19 population seemed to reveal that ALS patients with FVC <80% experienced a slower reduction in ALSFRS-R score after initiating edaravone treatment
- In the Study 19 placebo arm, bulbar-onset patients experienced a more rapid decline in ALSFRS-R score over time compared with limb-onset patients[c]
- Patients in both the bulbar[c]- and limb-onset groups experienced a slower reduction in ALSFRS-R score with edaravone treatment vs placebo through week 48
- In addition, after starting open-label treatment with edaravone, former placebo patients with either bulbar- or limb-onset disease seemed to demonstrate a slower reduction in ALSFRS-R score from baseline to week 48, and a notable change in the slope of the ALSFRS-R score-vs-time graph[c]
- Analysis of bulbar-onset patients with either FVC <80% or ≥80% seemed to indicate that both populations experienced a slower reduction in ALSFRS-R score with edaravone vs placebo[c]
- The limitations inherent with post hoc analyses should be considered when interpreting these results
- Further studies to assess bulbar function with edaravone are under consideration

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