A Post-hoc Analysis of the Edaravone Phase 3 Study 19: Regression Analyses to Examine Long-Term Efficacy

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BACKGROUND

- Amyotrophic lateral sclerosis (ALS) is a progressive and debilitating neurodegenerative disease in which the 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[2,3]
- Radicava® (edaravone), an FDA-approved ALS treatment, which has been an antioxidant free-radical scavenger that works to protect motor neurons from free-radical and oxidative stress damage[4]
- The efficacy and safety of edaravone were demonstrated in a Phase 3 study (Study 19; MCI-186-19), consisting of a 24-week, double-blind, placebo-controlled phase, followed by a 24-week open-label extension phase in which all subjects received active treatment[5,6]
- In the double-blind phase, edaravone was demonstrated to slow down the progression of disability in subjects with ALS – there was 33% less functional loss with edaravone vs placebo at 24 weeks – meeting its primary end point[5]
- The extension phase was designed to explore the long-term efficacy and safety of edaravone[6]
  - However, the open-label design precluded long-term comparison with placebo
- A post-hoc analysis from the double-blind phase, reported here, provides an alternative method for assessing the long-term efficacy of edaravone vs placebo

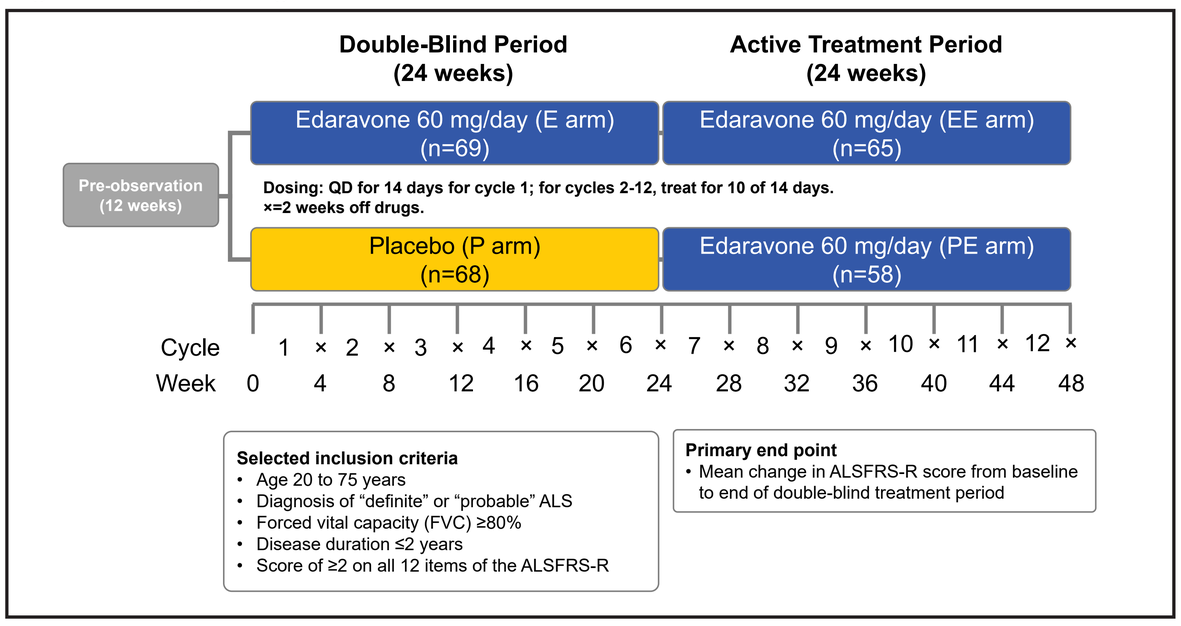
OBJECTIVE

- This post-hoc analysis imputed data on the effect of edaravone from the double-blind, placebo-controlled phase of Study 19 through week 48, as measured by scores on the revised ALS Functional Rating Scale (ALSFRS-R)

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 (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 long-term efficacy and safety of edaravone

Figure 1. Study design



EE=edavarone-edavarone; PE=placebo-edavarone.

RESULTS

- The baseline demographics and clinical characteristics were well balanced between treatment groups **(Table 1)**

Table 1: Baseline demographics and clinical characteristics (full analysis set)

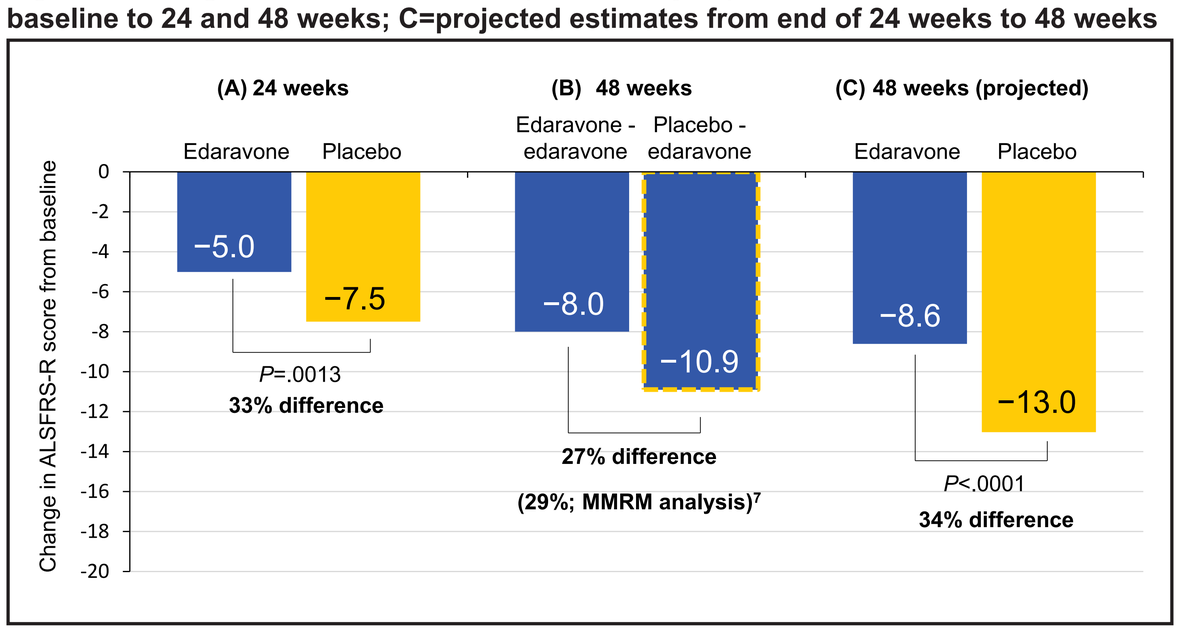
	Edaravone (n=69)	Placebo (n=68)
Gender, n (%)		
Men	38 (55)	41 (60)
Women	31 (45)	27 (40)
Mean age (SD), yr	60.5 (10)	60.1 (10)
Mean duration of disease (SD), yr	1.13 (0.5)	1.06 (0.5)
Initial symptom, n (%)		
Bulbar symptom	16 (23)	14 (21)
Limb symptom	53 (77)	54 (79)
ALS diagnostic criteria, n (%)[a]		
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).
SD=standard deviation.

- From baseline to week 24 (cycle 6), the least-squares mean change in ALSFRS-R score was −5.01 for edaravone and −7.50 for placebo, indicating a clinically meaningful difference of 33% (*P*=.0013) **(Figure 2)**
- At the end of week 48 (cycle 12), the change in ALSFRS-R score from baseline was −8.0 in subjects treated with edaravone for a total of 48 weeks (EE) vs −10.9 in subjects receiving placebo for 24 weeks, followed by 24 weeks of edaravone (P-E), a 27% difference **(Figure 2)**
- Projecting the results from the controlled, double-blind phase through week 48 (cycle 12) using multiple linear regression analysis, the functional decline remained significantly lower for edaravone vs placebo **(Figures 2 and 3)**
- The projected change in ALSFRS-R score at the end of week 48 (cycle 12) for edaravone treatment vs placebo was −8.61 vs −13.03, a 34% difference (*P*<.0001) **(Figure 2)**
  - Actual edaravone vs projected placebo at week 48 (cycle 12) was −8.02 vs −13.03, a 38% difference (*P*<.0001)
- The rate of decline in ALSFRS-R score was consistent for each group that received edaravone and decreased when placebo subjects began receiving edaravone in the open-label, active treatment phase **(Figure 3)**
  - ALSFRS-R slopes
    - Edaravone (baseline to cycle 6) – 0.718
    - Edaravone-edaravone (cycle 7 to cycle 12) – 0.653
    - Placebo (baseline to cycle 6) – 1.086
    - Placebo-edaravone (cycle 7 to cycle 12) – 0.638

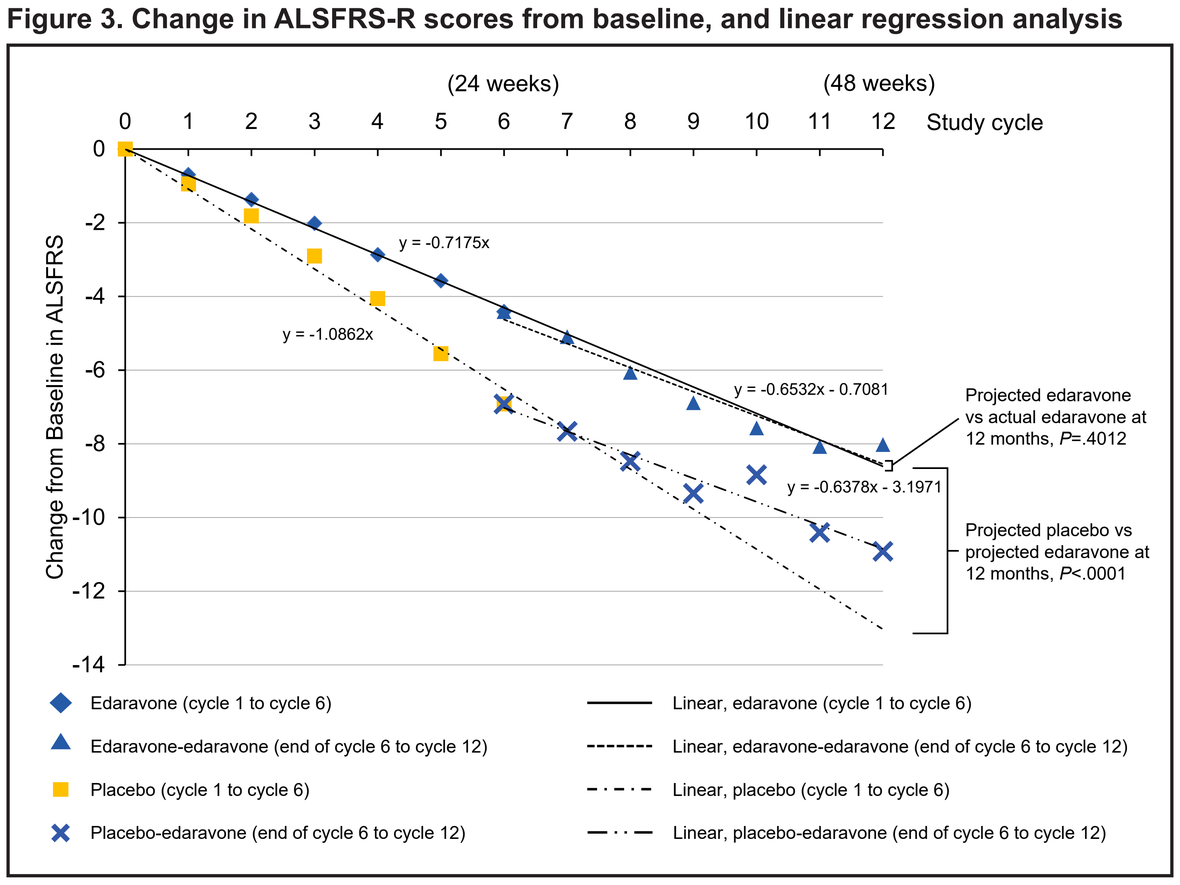
    } Change in slope after starting edaravone

Figure 2. Change in ALSFRS-R scores (LOCF analysis). A, B=actual treatment from baseline to 24 and 48 weeks; C=projected estimates from end of 24 weeks to 48 weeks



LOCF=last observation carry forward; MMRM=mixed-effect model repeated measurement.

Figure 3. Change in ALSFRS-R scores from baseline, and linear regression analysis



CONCLUSIONS

- Based on measured values and multiple linear regression analysis, the decline in ALSFRS-R score in the placebo group was greater than in either the projected or actual edaravone group through 12 months of treatment
- These post-hoc findings suggest that edaravone continues its treatment effect and maintains long-term efficacy for 12 months

REFERENCES

1. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med*. 2017;377:162-172.
2. Hardiman O, et al. Amyotrophic lateral sclerosis. *Nat Rev Dis Primers*. 2017;3:17085.
3. Scott A. Drug therapy: On the treatment trail for ALS. *Nature*. 2017;550:S120-S121.
4. Brooks BR, et al. Edaravone in the treatment of amyotrophic lateral sclerosis: efficacy and access to therapy – a roundtable discussion. *Am J Manag Care*. 2018;24:S175-S186.
5. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16:505-512.
6. Writing Group on Behalf of the Edaravone (MCI-186) ALS 19 Study Group. Open-label 24-week extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. *Amyotroph Lateral Sclero Frontotemporal Degener*. 2017;18:55-63.
7. Palumbo JM, et al. Long-term safety and efficacy of edaravone (MCI-186) for the treatment of amyotrophic lateral sclerosis (ALS). Presented at American Academy of Neurology Annual Meeting, Vancouver, BC, Canada. April 15-21, 2016. P3.190.

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