Toward More Efficient Clinical Trial Designs in ALS: Lessons From the Edaravone Development Program

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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[1,2]
- Clinical trials in ALS have been challenging to design for a variety of reasons[3]
  - Heterogeneity of symptoms
  - Variable rate of progression
  - Limitations of assessment tools
- The edaravone development program employed a strategic enrichment design to Study 19 (MCI-186-19) to address these challenges[3-5]
  - Enrichment was based on key learnings from a post-hoc analysis of the preceding Study 16[5-7]
  - The goal was to design a study in which a treatment effect could be documented within a 6-month timeframe utilizing scores on the ALS Functional Rating Scale-Revised (ALSFRS-R) as the primary end point
- Post-hoc assessments of Study 16 and Study 19 were conducted to investigate the influence of study design on the ability to detect a treatment effect

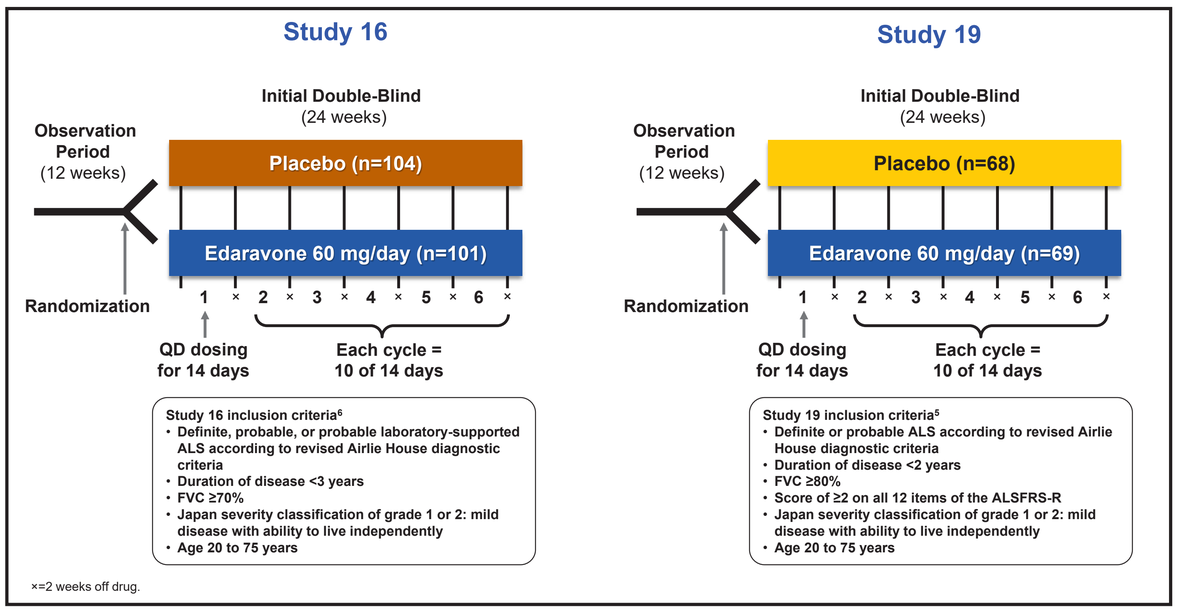
OBJECTIVE

- Post-hoc assessments of Study 16 and Study 19 were conducted to examine how differences in study design, specifically inclusion criteria, influenced the ability to detect a treatment effect, as assessed by scores on the ALSFRS-R

METHODS

- The study designs for Study 16 and Study 19 are shown in **Figure 1**
- Based on post-hoc analyses of Study 16, investigators utilized inclusion criteria in Study 19 in order to help enrich for a population that would more readily show a change in ALSFRS-R score during a 24-week trial **(Figure 1)**
  - Diagnostic criteria were restricted to definite or probable ALS (excluding subjects who had only probable laboratory-supported ALS)
  - Disease duration was shortened from <3 years to <2 years
  - Forced vital capacity (FVC) was increased from ≥70% to ≥80%
  - Subjects were required to have a score of ≥2 on all 12 items of the ALSFRS-R (all subjects were also required have a score of 4 on the respiratory items of the ALSFRS-R)
- Post-hoc analyses were conducted of the placebo arms from Study 16 and Study 19, analyzing the change in ALSFRS-R score from baseline to week 24 (end of cycle 6)
- Disease progression, based on changes in ALSFRS-R score from baseline to week 24, were defined as
  - No progression 0-point decline
  - Minimal progression ≤2-point decline
  - Slow progression ≤5-point decline
  - Significant progression ≥10-point decline

Figure 1. Study designs for Study 16 and Study 19



RESULTS

- There were 104 and 69 subjects in the placebo arm of Study 16 and Study 19, respectively **(Figure 1)**
- A larger proportion of placebo subjects in Study 16 (35%) than in Study 19 (13%) experienced minimal progression **(Table 1 and Figure 2)**
  - The subjects from Study 16 who experienced minimal progression averaged –0.13 points/month

Table 1. Disease progression in the placebo arms of Study 16 and Study 19

Progression	Study 16 (n=104) % (n)	Study 19 (n=69) % (n)
No progression (0-point decline)	17% (18)	6% (4)
Minimal progression (≤2-point decline)	35% (36)	13% (9)
Slow progression (≤5-point decline)	63% (65)	51% (35)
Significant progression (≥10-point decline)	24% (25)	24% (16)

- In PRO-ACT, the ALSFRS-R score has been shown to change by approximately –1 point per month in patients with ALS[8]
- In order to be able to measure a change in ALSFRS-R score during 24 weeks of therapy, ideally there would be a distribution of change in ALSFRS-R score similar to what is depicted in **Figure 2**
- Analyses were conducted of the distribution of changes from baseline to week 24 (end of cycle 6) in ALSFRS-R score in the placebo arms of each study (**Figure 3**; each circle represents one patient)
- The mode for the Study 16 placebo subject distribution was 0 points, as compared with a value of –4 points for Study 19 placebo subjects **(Figure 3)**
- The distribution for Study 16 placebo subjects was further analyzed by determining the number of subjects who would not have qualified for participation in Study 19 based on the inclusion criteria for Study 19 **(Figure 4)**
  - 72 of the 104 Study 16 placebo subjects would not have been eligible for Study 19
  - Study 16 subjects who were distributed mainly in the slow progression range were those with a score of 1 on at least 1 individual item of the ALSFRS-R, those with a "possible" or "probable" lab-supported diagnosis, and those who were ≥2 years out since onset of symptoms
  - However, subjects with FVC <80% were distributed fairly evenly throughout the range of ALSFRS-R progression values

Figure 2. Hypothetical "ideal" distribution of changes in ALSFRS-R score at week 24

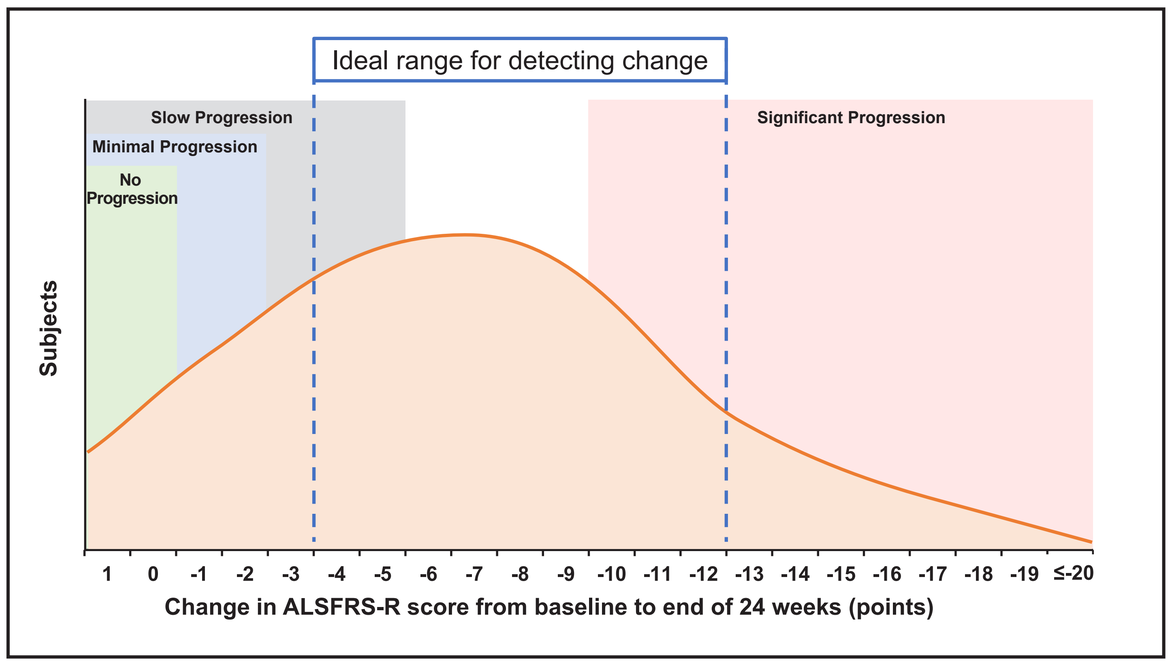


Figure 3. Study 16 and Study 19 distribution of changes in ALSFRS-R score at week 24: Placebo subjects

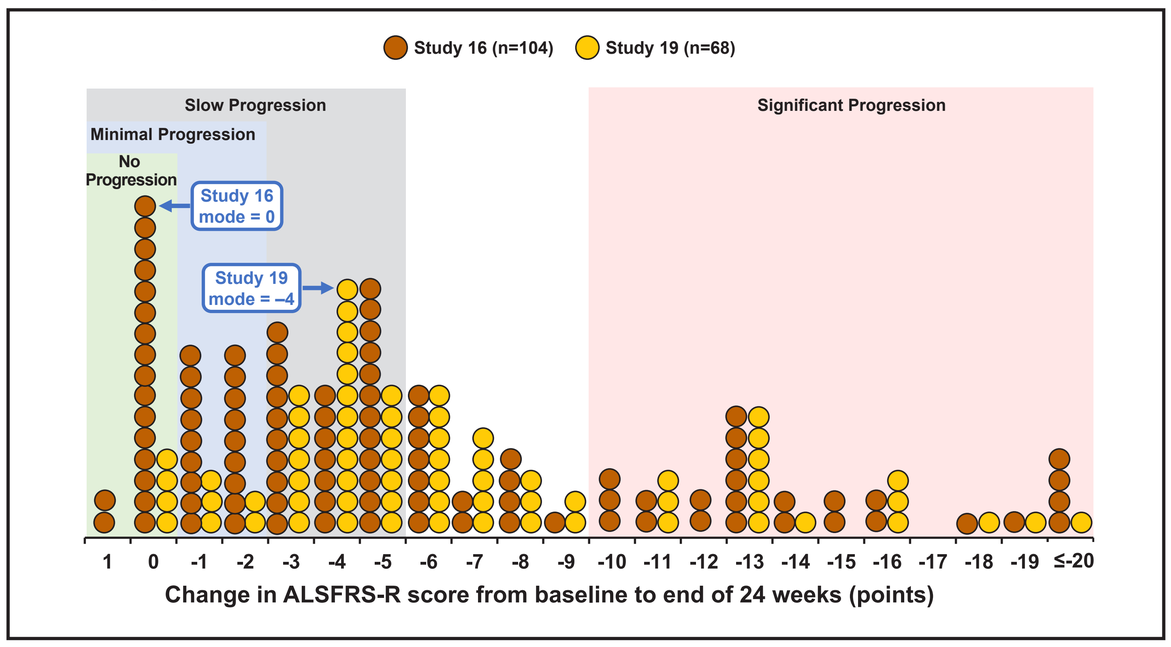
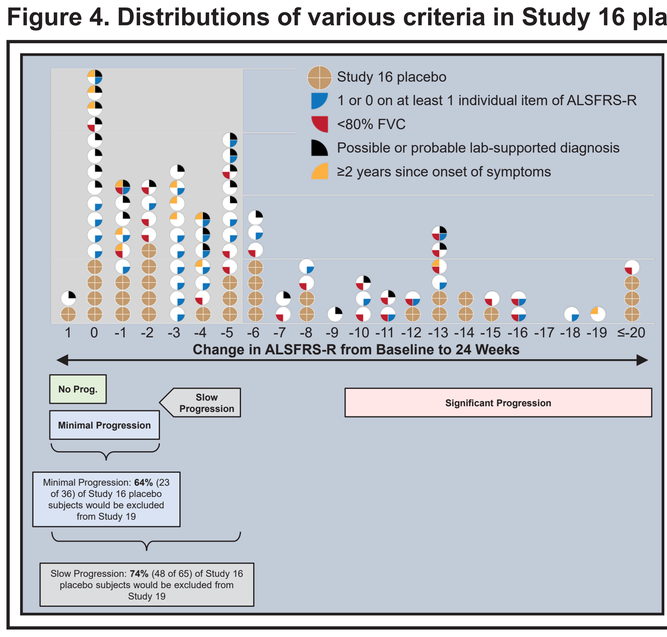


Figure 4. Distributions of various criteria in Study 16 placebo subjects



72 of the 104 Study 16 placebo subjects would not have been eligible for Study 19

By an Individual Inclusion Criterion
65% of subjects had 1 inclusion criterion that would have excluded them from Study 19 enrollment (47 subjects)
- 20 subjects (19.23%) 1 or 0 on at least 1 individual item of ALSFRS-R
- 11 subjects (10.58%) <80% FVC
- 13 subjects (12.5%) Possible or probable lab-supported diagnosis
- 3 subjects (2.88%) ≥2 years since onset of symptoms

By Multiple Inclusion Criteria
35% had multiple inclusion criteria that would have excluded them from Study 19 enrollment (25 subjects)
- 21 subjects had 2 inclusion criteria
- 3 subjects had 3 inclusion criteria
- 1 subject had 4 inclusion criteria

Of these subjects:
- 35 subjects (33.66%) 1 or 0 on at least 1 individual item of ALSFRS-R
- 24 subjects (23.08%) <80% FVC
- 28 subjects (26.92%) Possible or probable lab-supported diagnosis
- 13 subjects (12.5%) ≥2 years since onset of symptoms

CONCLUSIONS

- It is likely that a study enrichment that maximizes the propensity for dynamic change—and thus the potential for an experimental therapy to modify that change—is important for efficient clinical trial design in ALS
- Post-hoc analysis demonstrated that Study 16 included a large proportion of slow progressors
  - More than 1/3 of the placebo group deteriorated by an average of 0.13 points per month
- The large proportion of subjects with negligible or minimal progression as measured by the ALSFRS-R over 6 months in Study 16 made it virtually impossible to detect a treatment effect for an agent that does not provide acute symptomatic benefit such as edaravone
- By applying these learnings and modifying the inclusion criteria of Study 16 for the Study 19 enrichment strategy design, investigators were able to decrease the proportion of slow progressors in Study 19 and enhance the ability to show the effects of edaravone treatment on ALS disease progression

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