Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial

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Summary

Background In a previous phase 3 study in patients with amyotrophic lateral sclerosis (ALS), edaravone did not show a significant difference in the Revised ALS Functional Rating Scale (ALSFRS-R) score compared with placebo. Post-hoc analysis of these data revealed that patients in an early stage with definite or probable diagnosis of ALS, defined by the revised El Escorial criteria, who met a select set of inclusion criteria showed a greater magnitude of effect than did the full study population. We aimed to substantiate this post-hoc result and assess safety and efficacy of edaravone in a phase 3 trial that focused on patients with early stage ALS who met the post-hoc analysis inclusion criteria.

Methods In this phase 3, randomised, double-blind, parallel-group study, patients aged 20–75 years with ALS of grade 1 or 2 in the Japan ALS Severity Classification, scores of at least 2 points on all 12 items of ALSFRS-R, forced vital capacity of 80% or more, definite or probable ALS according to the revised El Escorial criteria, and disease duration of 2 years or less were recruited from 31 hospitals in Japan. Eligible patients also had a decrease of 1–4 points in the ALSFRS-R score during a 12-week observation period before randomisation. Patients meeting all criteria were then randomly assigned 1:1 to receive 60 mg intravenous edaravone or intravenous saline placebo for 6 cycles (4 weeks per cycle with 2 weeks on, 2 weeks off) for a total treatment duration of 24 weeks. In cycle 1, the study drug or placebo was administered once per day for 14 days within a 14 day period, followed by the drug-free period. In cycle 2 and thereafter, the study drug or placebo was administered for 10 days within a 14 day period, followed by a 2 week drug-free period. Participants and investigators, including those assessing outcomes, were masked to treatment allocation. The primary efficacy outcome was the change in ALSFRS-R score from the baseline to 24 weeks (or at discontinuation if this was after the third cycle) after randomisation. The primary outcome was assessed in all patients who had received at least one treatment infusion, had at least one assessment post-baseline, and reached the end of cycle 3. For patients with missing values at the end of cycle 6, data were imputed by the last observation carried forward (LOCF) method, provided the patients had completed at least cycle 3. Safety was assessed in all patients who had received at least one treatment infusion and had at least one assessment post-baseline. This trial is registered with ClinicalTrials.gov, NCT01492686.

Findings Between Nov 28, 2011, and Sept 3, 2014, we screened 213 patients, and enrolled 192 as potential participants. Of these, 137 patients completed the observation period: 69 were randomly assigned to receive edaravone, and 68 were randomly assigned to receive placebo. 68 patients taking edaravone and 66 taking placebo were included in the primary efficacy analysis. For the primary outcome, the change in ALSFRS-R score was −5·01 (SE 0·64) in the edavarone group and −7·50 (0·66) in the placebo group. The least-squares mean difference between groups was 2·49 (SE 0·76, 95% CI 0·99–3·98; p=0·0013) in favour of edaravone. Treatment-emergent adverse events were reported in 58 (84%) patients receiving edaravone and 57 (84%) patients receiving placebo. 11 (16%) patients taking edaravone and 16 (24%) taking placebo had serious adverse events, and one (1%) patient receiving edaravone and four (6%) patients receiving placebo had adverse events (one dysphagia in edaravone group and one dyspnoea, two respiratory disorder, and one rash in the placebo group) that led to withdrawal.

Interpretation Edaravone showed efficacy in a small subset of people with ALS who met criteria identified in post-hoc analysis of a previous phase 3 study, showing a significantly smaller decline of ALSFRS-R score compared with placebo. There is no indication that edaravone might be effective in a wider population of patients with ALS who do not meet the criteria.

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See Online for appendix

Introduction

The cause of amyotrophic lateral sclerosis (ALS) remains unknown, except for familial forms of ALS including those caused by mutations in *SOD1*[1] or *C9orf72*.[2,3] However, oxidative stress caused by free radicals might be an essential factor in the progression of the disease, being involved not only in motor neuron degeneration, but also in glial and endothelial cell dysfunctions.[4,5] Oxidative

Research in context

Evidence before this study

Edaravone was discovered and developed as a potential free radical scavenger to reduce oxidative stress. As edaravone showed a protective effect on endothelial and neuronal cells exposed to high oxidative stress in animal models, it was initially developed for treatment of acute ischaemic stroke, and was approved for this indication in Japan in 2001. Animal models suggested potential benefit of edaravone to treat amyotrophic lateral sclerosis (ALS), and an open-label, phase 2 study of edaravone in patients with ALS showed a decreased concentration of an oxidative stress biomarker (3-nitrotyrosine), and a numerical decrease in Revised ALS Functional Rating Scale (ALSFRS-R) scores for 6 months after initiation of edaravone treatment, although this effect was not tested for significance. The first phase 3 study did not show a significant difference in the ALSFRS-R score between patients receiving edaravone and placebo. However, post-hoc analyses of this study identified a subpopulation in which edaravone did show efficacy.

Added value of this study

The safety and efficacy of edaravone were examined in this placebo-controlled, double-blind phase 3 study for patients with ALS who met all of the following criteria identified in post-hoc analyses of the previous phase 3 trial: scores of at least 2 points on all 12 items of ALSFRS-R, forced vital capacity of at least 80%, definite or probable ALS (El Escorial and revised Airlie House diagnostic criteria), and disease duration of 2 years or less. The primary endpoint, change in ALSFRS-R at 24 weeks, was significantly smaller in the patients receiving edaravone, by comparison with placebo. The results of the secondary endpoints Modified Norris Scale (total) and ALS Assessment Questionnaire (ALSAQ-40), also supported the primary result.

Implications of all the available evidence

In a small, well defined group of patients with early stage ALS, the progression of ALS symptoms was slowed by edaravone. However, the effect of edaravone administration on the long term survival rate, the efficacy of edaravone in a wider population of patients with ALS, and the efficacy in patients with advanced disease were not considered in this study.

stress biomarkers (3-nitrotyrosine, coenzyme Q10, 8-hydroxydeoxyguanosine, and 4-hydroxy-2,3-nonenal) are higher in people with ALS than in people without,[6–10] and as ALS progresses, nutritional deficiency, cachexia, and psychological stress might also contribute to increased oxidative stress biomarkers.[4] Edaravone (also known as MCI-186), a free-radical scavenger of peroxyl radicals and peroxynitrite, has been shown to inhibit motor neuron death in animal models by reducing oxidative stress.[11–13] Therefore, edaravone might work in a similar way to ameliorate the disease progression of ALS. Edaravone has been given to 1·7 million patients with acute ischaemic stroke in Japan since 2001 for improvement of neurological symptoms, disruption of daily activities, and functional impairment associated with acute ischaemic stroke.[14]

In an open-label phase 2 study of edaravone in patients with ALS, the change in Revised ALS Functional Rating Scale (ALSFRS-R) score[15,16] was significantly less during the 6 month treatment period with 60 mg edaravone compared with the 6 months before the start of edaravone.[17] The concentration of 3-nitrotyrosine was low in the CSF of almost all patients in the phase 2 study, suggesting that edaravone might protect neuronal cells from oxidative stress in this population.[17] Based on these findings, the first placebo-controlled phase 3 study of edaravone was done over 24 weeks of treatment. However, there was no significant difference in the primary endpoint of ALSFRS-R score for patients receiving edaravone compared with placebo.[18] With the aim of finding out whether there is a subgroup of patients with ALS in whom edaravone might be effective in slowing disease progression, we did a post-hoc analysis that suggested a potential benefit of edaravone in patients with scores of 2 or more on all items of ALSFRS-R, forced vital capacity (FVC) of at least 80% at baseline, definite or probable ALS (El Escorial and revised Airlie House criteria[19]), and disease duration of 2 years or less. Since post-hoc analyses of clinical studies have limitations in their interpretability, in this phase 3 study we assessed safety and efficacy of edaravone in a prospectively defined population of patients meeting all these criteria.

Methods

Study design and participants

We did a randomised, double-blind, parallel-group, placebo-controlled study in patients recruited from 31 hospitals in Japan. Eligible patients were aged 20–75 years with a diagnosis of ALS with independent living status (grade 1 or 2 in the Japan ALS Severity Classification[18]) confirmed by local clinicians at time of enrolment, and decrease in the ALSFRS-R score of 1–4 during a 12-week observation period. Based on the post-hoc analysis findings of the first phase 3 study, eligible patients also had scores of at least 2 on all 12 items of ALSFRS-R, FVC of at least 80%, definite or probable ALS according to the El Escorial and revised Airlie House criteria[19]), and duration of disease from the first symptom (any ALS symptom) of 2 years or less.

Patients were excluded before randomisation if they had a score of 3 or less on ALSFRS-R items for dyspnoea,

orthopnea, or respiratory insufficiency; history of spinal surgery after onset of ALS; or creatinine clearance 50 mL/min or less. Patients who had already been given riluzole[20] could continue to receive riluzole provided that the regimen remained unchanged, but initiation of riluzole after the start of the observation period was prohibited.

The study was done in compliance with the Japanese Ministerial Ordinance on Good Clinical Practice, and in accordance with the ethical principles of the Declaration of Helsinki. An institutional review board approved the protocol at each site. All patients provided written informed consent at study entry.

Randomisation and masking

After the 12-week observation period, eligible patients were randomly assigned to receive edaravone or placebo (1:1) by the independent registration centre. To achieve an overall balance across important prognostic factors, a dynamic allocation of the minimisation method was used with stratification for ALS diagnosis according to El Escorial and revised Airlie House criteria (definite *vs* probable), change in ALSFRS-R score during the observation period (–1 or –2 *vs* –3 or –4), and age (65–75 *vs* 20–64 years). Participating investigators registered patients in accordance with the inclusion and exclusion criteria and also assessed safety and efficacy, but were masked to treatment.

Edaravone and placebo were provided in ampules that were indistinguishable in appearance and packaging, and contained 60 mg edaravone or saline only (placebo) to be diluted in approximately 100 mL saline. Only authorised people (excluding the funder and the investigators) were able to access the key code until unblinding, and these people were not involved in any other aspect of the study.

Procedures

Before randomisation, potential participants fulfilling selection criteria entered a 12-week observation period. Only patients with a decrease in ALSFRS-R score of between 1 and 4 points during this period were included and randomly assigned to treatment groups for the double-blind treatment period of 24 weeks (6 cycles). In cycle 1, the study drug was administered for 14 consecutive days followed by a 2 week drug-free period. In cycle 2 and thereafter, the study drug was administered for 10 days within a 14 day period, followed by a 2 week drug-free period. All patients who completed cycle 6 were offered open-label extension treatment with edaravone for an additional 6 cycles, up to cycle 12 (unpublished).

During the treatment portion of each cycle, edaravone (60 mg, diluted with approximately 100 mL saline) or placebo (equivalent amount of saline) was administered once a day via 60-min intravenous infusion by the investigator, or by a doctor or nurse delegated by the investigator (all of whom were blinded to treatment allocation).

Outcomes

The primary efficacy endpoint was the change in ALSFRS-R score from the baseline to the end of cycle 6 (or at discontinuation if this was after the third cycle) after randomisation. The assessments were done before the 12-week observation period, before the start of cycle 1, and at the end of each cycle (after the 2-week drug-free period and before the first dose of the next cycle).

Secondary endpoints included change in FVC; Modified Norris Scale scores (limb, bulbar, and total);[21,22] ALS Assessment Questionnaire (ALSAQ-40) score;[23,24] ALS severity classification; and grip and pinch strength. Time to death or time to a specified state of disease progression (defined as disability of independent ambulation, loss of upper-limb function, tracheotomy, use of a respirator, use of tube feeding, or loss of useful speech) occurring during the 6 cycles was also deemed a secondary endpoint.

Safety endpoints included the incidence of adverse events, adverse drug reactions, clinical laboratory tests (haematology, blood biochemistry, and urinalysis) and sensory tests throughout the 6 cycles. A Data Safety Monitoring Committee, which was able to access unmasked safety data if necessary, monitored safety throughout the study.

Statistical analysis

Based on the post-hoc findings in the previous phase 3 study, we calculated that a sample size of 128 patients (64 per group) was required to provide 80% power to detect an adjusted mean difference between groups of 3·0 points on the ALSFRS-R score at cycle 6 (24 weeks) with an SD of 6·0 points for analysis of the primary endpoint.

The primary endpoint was analysed in the full-analysis set, defined as all randomly assigned patients who received at least one dose of study drug and had at least one efficacy assessment post baseline and reached the end of cycle 3. For patients with missing values at the end of cycle 6, data were imputed by the last observation carried forward (LOCF) method, provided the patients had completed at least cycle 3. For the primary efficacy analysis, the change from baseline in cycle 1 to the end of cycle 6 in ALSFRS-R score during double-blind treatment was compared between treatment groups using ANOVA with the treatment group and three dynamic allocation factors. Statistical significance was set at a two-sided level of 0·05. We did a sensitivity analysis using ANOVA to check the robustness of imputation of missing data for the primary analysis result. Rather than using the LOCF method, missing data at the end of cycle 6 were imputed by linear regression, using all available data for each patient whose data at the end of cycle 6 was missing and taking into account ALS disease progression. We estimated the least-squares mean difference between

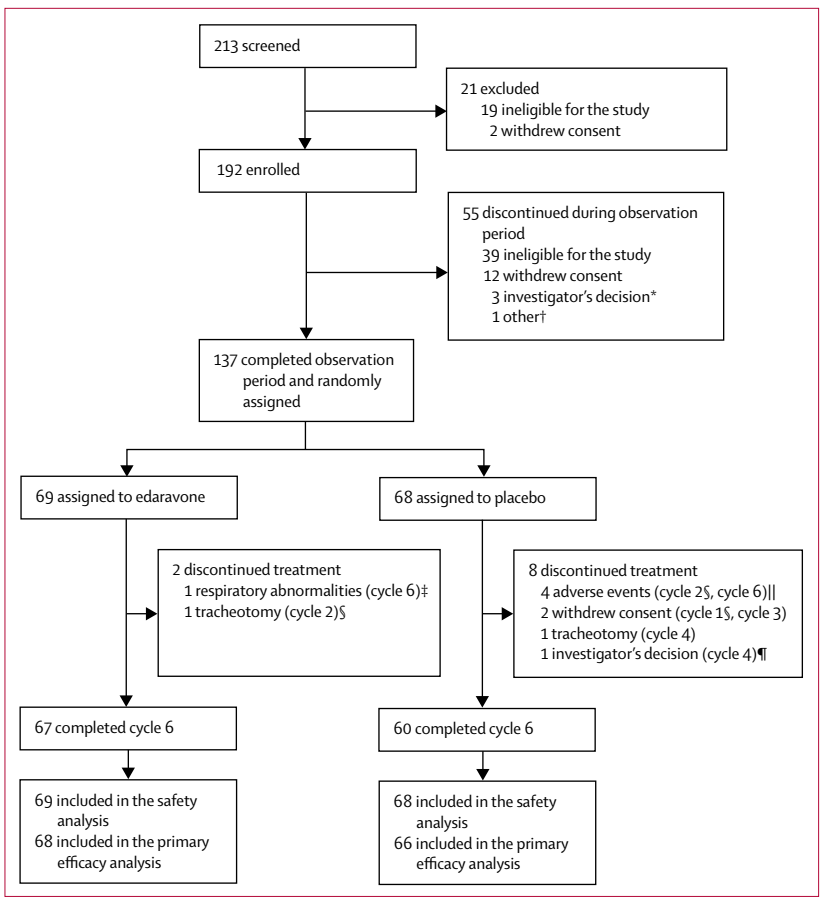

Figure 1: **Trial profile**
FVC=forced vital capacity (%). $PaCO_2$=partial pressure of carbon dioxide in arterial blood. *Owing to worsening of amyotrophic lateral sclerosis. †Patient failed to return to hospital. ‡FVC of 50% or lower and $PaCO_2$ 45 mm Hg or higher. No randomised patients were excluded from the full-analysis set or from the safety analysis set. §Patients who did not reach the end of cycle 3 (one in the edaravone group and two in the placebo group) were excluded from the analysis set used for the primary analysis. ||1 of 3 patients that discontinued in cycle 6 had FVC of 50% or lower and PaCO2 45 mm Hg or higher. ¶Owing to complications of frontotemporal dementia, making it difficult to assess the patient accurately.

edaravone and placebo in the change from baseline to the end of cycle 6 for the primary efficacy endpoint. The LOCF method used to impute missing data involves the assumption that the outcome is constant after withdrawal, and it is well known that this can generate some bias and affect the type 1 error rate for the treatment effect.[25–27] Therefore, we did post-hoc analyses using both ANOVA with LOCF using all available data for each patient and the mixed effects model for repeated measures (MMRM), which can address all available post-baseline data.

We analysed secondary efficacy endpoints except for ALS severity classification by the same method of ANOVA for the primary endpoint; however, we did not adjust for multiplicity. For the secondary endpoint of time to death or to a specified state of disease progression, we did Kaplan-Meier plot, log-rank test and generalised Wilcoxon test. For censored patients, we used time to the last observation date for the Kaplan-Meier plot. We summarised ALS severity classification from baseline to the end of cycle 6 using a shift table by treatment groups. Safety was examined using the safety analysis set, defined as any patient who had received at least one dose of edaravone or placebo and who had at least one safety assessment post baseline. This study is registered with ClinicalTrials.gov, number NCT01492686.

Role of the funding source

The study funder (Mitsubishi Tanabe Pharma Corporation) was involved in study design, study monitoring, data collection and management, statistical analysis, data interpretation, and writing of the draft report of this study. All authors had access to the data table listings (prepared by Mitsubishi Tanabe Pharma Corporation), which were used to prepare the Results and Discussion sections of this report. The corresponding author had full access to all of the data in this study and takes final responsibility for the decision to submit this report for publication.

Results

Between Nov 28, 2011, and Sept 3, 2014, we screened 213 patients, 137 of whom completed the observation period and were randomly assigned to receive edaravone (n=69) or placebo (n=68; figure 1). Two patients in the edaravone group and eight patients in the placebo group discontinued the study in accordance with discontinuation criteria before completion of cycle 6. One patient in the edaravone group and two patients in the placebo group did not reach the end of cycle 3, so 134 patients were included in the primary analysis (68 in the edaravone group and 66 in the placebo group). Overall, the demographics and baseline characteristics of patients were well balanced between the treatment groups except for sex and ALS severity, which showed an imbalance skewed towards male sex and grade 2 ALS severity (table 1).

Mean ALSFRS-R scores through the study period are shown in figure 2 by treatment group. From baseline to the end of cycle 6 (or discontinuation), the least-squares mean difference in mean ALSFRS-R scores between treatment groups was 2·49 in favour of edaravone (95% CI 0·99–3·98, p=0·0013; table 2).

Assessments of Modified Norris Scale (total) favoured edaravone compared with placebo (least-squares mean difference 4·89, SE 2·35; p=0·0393). Deterioration in quality of life, shown by ALSAQ-40, was lower in patients receiving edaravone compared with patients receiving placebo (least-squares mean difference –8·79, SE 4·03; p=0·0309). There was no difference in FVC, Modified Norris Scale (limb or bulbar), grip strength, pinch strength (table 2), or ALS severity classification at the end of cycle 6 (appendix) in patients given edaravone compared with placebo. Death or a specified state of disease progression occurred in two patients in the edaravone group (one tracheotomy and one loss of useful

	Edaravone group (n=69)	Placebo group (n=68)
Sex		
Men	38 (55%)	41 (60%)
Women	31 (45%)	27 (40%)
Age, years	60·5 (10)	60·1 (10)
Younger than 65 years*	46 (67%)	46 (68%)
65 years or older*	23 (33%)	22 (32%)
Bodyweight, kg	57·9 (12·9)	57·8 (9·3)
Height, cm	161·8 (9·5)	162·5 (8·4)
BMI, kg/m²†	21·9 (3·6)	21·8 (2·7)
ALS diagnosis		
Sporadic	68 (99%)	66 (97%)
Familial	1 (1%)	2 (3%)
ALS diagnostic criteria‡		
Definite*	28 (41%)	27 (40%)
Probable*	41 (59%)	41 (60%)
ALS severity§		
Grade 1	22 (32%)	16 (24%)
Grade 2	47 (68%)	52 (76%)
Duration of disease, years	1·13 (0·5)	1·06 (0·5)
Initial symptom		
Bulbar onset	16 (23%)	14 (21%)
Limb onset	53 (77%)	54 (79%)
ALSFRS-R score		
Before observation period	43·6 (2·2)	43·5 (2·2)
At baseline (at the end of 12 week observation period)	41·9 (2·4)	41·8 (2·2)
Change about observation period		
−4 or −3*	12 (17%)	11 (16%)
−2 or −1*	57 (83%)	57 (84%)
Riluzole use		
Yes	63 (91%)	62 (91%)
No	6 (9%)	6 (9%)

Data are n (%) or mean (SD). ALS=amyotrophic lateral sclerosis. ALSFRS-R=Revised ALS Functional Rating Scale. *Factor used in dynamic allocation. †Post-hoc assessment. ‡According to revised El Escorial criteria. §According to Japan ALS severity classification (grade 1–5, grade 5 most severe).

***Table 1*: Demographics and baseline clinical characteristics**

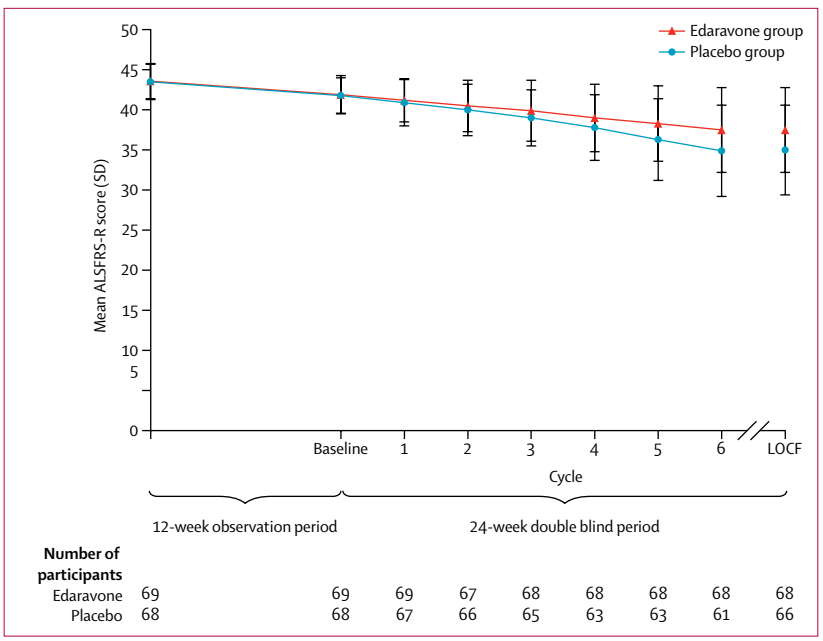

***Figure 2*: Mean ALSFRS-R scores during treatment**

For patients with missing values at the end of cycle 6, data were imputed by the LOCF method, provided that they had completed at least cycle 3. ALS=amyotrophic lateral sclerosis. ALSFRS-R=Revised ALS Functional Rating Scale. LOCF=last observation carried forward. One patient's evaluation at the end of cycle 2 was excluded from analysis as the clinician assessing ALSFRS-R score did not have adequate training.

speech) and in six patients in the placebo group (three loss of useful speech, two disabilities of independent ambulation, and one use of tube feeding). The difference between groups for this secondary endpoint was not significant (log-rank test p=0·13, generalised Wilcoxon test p=0·14).

The number of patients reporting at least one adverse event did not differ significantly between the two groups (58 [84%] of 69 patients in the edaravone group *vs* 57 [84%] of 68 patients in the placebo group). 11 (16%) of 69 patients in the edaravone group and 16 (24%) of 68 patients in the placebo group encountered at least one serious adverse event. No deaths were reported during the 24-week double-blind period. One patient in the edaravone group and four patients in the placebo group had adverse events leading to discontinuation (one dysphagia in the edaravone group and one dyspnoea, two respiratory disorder, and one rash in the placebo group. Adverse events reported by at least four patients (5%) of either group are listed in table 3, along with serious adverse events reported by at least two patients in either group. Adverse events during the 24-week double blind period with a reported incidence of at least 10% were contusion, constipation, and dysphagia in both groups, and dermatitis contact in the edaravone group. The only serious adverse event with a reported incidence of 5% or over was dysphagia, observed in both groups. No notable differences in changes of laboratory measurements and sensory tests were observed between the groups (data not shown).

Two (3%) of 69 patients in the edaravone group had adverse drug reactions (three events: abdominal discomfort, eczema, and abnormal liver function test) and five (7%) of 68 patients in the placebo group had adverse drug reactions (seven events: dizziness, constipation, rash, chondrocalcinosis pyrophosphate, blood bilirubin increased, blood creatine phosphokinase increased, and abnormal liver function test). No serious adverse drug reactions were reported from either group.

In the sensitivity analysis (with data imputation by linear regression using all available data for each patient whose data at the end of cycle 6 were missing), the least-squares mean difference between treatment groups was similar to the primary outcome result at 2·67 (SE 0·80, 95% CI 1·09–4·25; p=0·0011). In post-hoc analyses

	Least-squares mean change		Least-squares mean difference	p value*
	Edaravone (n)	Placebo (n)		
Primary endpoint				
ALSFRS-R score	−5·01, 0·64 (68)†	−7·50, 0·66 (66)†	2·49, 0·76 (0·99 to 3·98)	0·0013
Secondary endpoints				
FVC (%)	−15·61, 2·41 (67)†‡	−20·40, 2·48 (66)†	4·78, 2·84 (−0·83 to 10·40)	0·0942
Modified Norris Scale scores				
Total	−15·91, 1·97 (68)†	−20·80, 2·06 (63)†‡	4·89, 2·35 (0·24 to 9·54)	0·0393
Limb scale	−11·47, 1·61	−14·91, 1·68	3·44, 1·92 (−0·36 to 7·24)	0·0757
Bulbar scale	−4·44, 0·76	−5·89, 0·79	1·46, 0·90 (−0·33 to 3·24)	0·1092
ALSAQ-40 score	17·25, 3·39 (68)†	26·04, 3·53 (64)†‡	−8·79, 4·03 (−16·76 to −0·82)	0·0309
Grip strength (kg)§	−4·08, 0·54 (68)†	−4·19, 0·56 (66)†	0·11, 0·64 (−1·15 to 1·38)	0·8583
Pinch strength (kg)§	−0·78, 0·14 (68)†	−0·88, 0·14 (66)†	0·10, 0·16 (−0·23 to 0·42)	0·5478

Data are least-squares mean change, SE (n); or least-squares mean difference, SE (95% CI). ALS=amyotrophic lateral sclerosis. ALSAQ-40=ALS Assessment Questionnaire. ALSFRS-R=Revised ALS Functional Rating Scale. FVC=forced vital capacity (%). LOCF=last observation carried forward. *Compared between treatment groups using an ANOVA with treatment group and three dynamic allocation factors.†The numbers of patients are different from full-analysis set, because for patients with missing values at the end of cycle 6, data were imputed by the last observation carried forward (LOCF) method, provided that they had completed at least cycle 3. In the analysis of the primary outcome, patients who did not reach the end of cycle 3 (1 in the edaravone group and 2 in the placebo group) were excluded from the full-analysis set (69 in edaravone group and 68 in placebo group). ‡The numbers of patients are different from full-analysis set, because of missing data (one FVC score in edaravone group, three Modified Norris Scale scores in placebo group, and two ALSAQ-40 scores in placebo group). §Mean for the left and right hands. ALSFRS-R scores 0–48 (best). Modified Norris Scale scores 0–102 (best). Modified Norris Scale scores (Limb scale) 0–63 (best). Modified Norris Scale scores (Bulbar scale) 0–39 (best). ALSAQ-40 score 200–40 (best).

***Table 2*: Primary and secondary endpoints**

	Adverse events		Serious adverse events	
	Edaravone group (n=69)	Placebo group (n=68)	Edaravone group (n=69)	Placebo group (n=68)
Any	58 (84%)	57 (84%)	11 (16%)	16 (24%)
Contusion	13 (19%)	9 (13%)	0	1 (2%)
Constipation	8 (12%)	8 (12%)	0	0
Dermatitis contact	8 (12%)	3 (4%)	0	0
Dysphagia	8 (12%)	10 (15%)	8 (12%)	8 (12%)
Eczema	5 (7%)	2 (3%)	0	0
Insomnia	5 (7%)	4 (6%)	0	0
Upper respiratory tract inflammation	5 (7%)	2 (3%)	0	0
Back pain	4 (6%)	1 (2%)	0	0
Headache	4 (6%)	5 (7%)	0	0
Myalgia	4 (6%)	1 (2%)	0	0
Nasopharyngitis	3 (4%)	5 (7%)	0	0
Respiratory disorder	3 (4%)	2 (3%)	2 (3%)	2 (3%)
Diarrhoea	2 (3%)	4 (6%)	0	0
Speech disorder	1 (1%)	2 (3%)	1 (1%)	2 (3%)
Pneumonia aspiration	0	2 (3%)	0	2 (3%)

Data are n (%). Includes all adverse events that had occurred in at least 5% of patients or were rated as serious adverse events in more than two patients in either treatment group during the specified study period. Adverse events were defined using the Medical Dictionary for Regulatory Activities, Japanese Version 17.0. Serious adverse events were defined as fatal, life-threatening, causing or potentially causing disability, or causing or prolonging hospitalisation.

***Table 3*: Adverse events**

to assess bias generated by the LOCF method used to impute missing data, the least-squares mean was 2·37 (SE 0·75, p=0·0019) from ANOVA with LOCF using all available data for each patient and 2·81 (0·78, p=0·0004) from MMRM.

Discussion

In this phase 3 study, the difference in the ALSFRS-R score was significant after treatment with edaravone compared with placebo in a well defined population of patients with ALS. The results of post-hoc analyses using ANOVA with LOCF using all available data for each patient and MMRM to assess bias generated by the LOCF method, were consistent with the result of the primary outcome.

Mean ALSFRS-R score in patients receiving edaravone at the end of cycle 6 (37·5, SD 5·3) was similar to the mean ALSFRS-R score in the patients receiving placebo at the end of cycle 4 (37·8, 4·1). A survey of clinicians by Castrillo-Viguera and colleagues[28] suggested that suppression of ALSFRS-R score by 20% or more is clinically meaningful. In this second phase 3 study, the difference in the ALSFRS-R score between the edaravone and placebo groups amounted to 33% (derived from the difference between the edaravone and placebo groups [2·49/change in placebo group 7·50), although it is important to note that direct comparison between the results of our study and this survey requires careful consideration, since patients in the study had to meet strict inclusion criteria. The significant difference in the total Modified Norris Scale and ALSAQ-40 score (secondary outcomes) also support the primary analysis result.

It should be noted that this study was focused on patients in an early stage with a definite or probable diagnosis of ALS and therefore had several limitations. In particular, the efficacy of edaravone was not shown in the previous phase 3 study, but was prospectively reported in this study in patients meeting strict inclusion criteria chosen according to the results of post-hoc

analyses of the previous phase 3 study. Thus, the efficacy of edaravone has been substantiated only in the patients specifically investigated in this study. Numbers of adverse events and the changes of laboratory measurements were similar in the two groups. However, it should be noted that patients with moderate to severe renal impairment (ie, creatinine clearance 50 mL/min or less) were excluded from this study.

Because edaravone was expected to suppress degeneration and loss of motor neurons, this study was focused on the maintenance of function and quality of life in early stage patients with a definite or probable diagnosis of ALS, and it did not establish whether or not long term edaravone therapy prolongs survival. Although no safety problems that required careful attention were identified in the patients given edaravone, phase 3 studies that assess ALSFRS-R slope and survival should be done to assess long term safety and efficacy. Oxidative stress might play a part in ALS from the early stage through to the advanced stage.[7] Whether edaravone might be safe and effective in a broader population of patients with ALS in the advanced stage would require further study.

Contributors

KA, MAo, ST, YI, and GS contributed to the study design, and revision of the manuscript. MTo contributed to study design, revision of manuscript, and committee for assessment at registration of all patients. CH contributed to study design, statistical analysis, and revision of manuscript. MTa contributed to the initial study concept, drafting and revision of manuscript. MAk was the corresponding author, and did initial study concept, drafting, writing and revision of manuscript, and acquisition of data. KN drafted and revised the manuscript. FT did statistical analysis and revision of the manuscript. KK did study design, revision of manuscript, and review of the safety of patients who had serious adverse events. HY contributed to study design, revision of manuscript, committee for assessment at registration of all patients, and review of the safety of all patients who had serious adverse events.

Edaravone (MCI-186) ALS 19 Study Writing Group

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Declaration of interests

KA reports personal fees from Mitsubishi Tanabe. MAo reports grants from the Ministry of Health Labor and Welfare of Japan, Japan Society for the Promotion of Science, National Center of Neurology and Psychiatry, the Ministry of Education, Culture, Sports, Science and Technology of Japan, Japan Agency for Medical Research and Development. MAo also reports personal fees from Eisai, Mitsubishi Tanabe, Astellas, Takeda, Sanofi, Novartis, and Sumitomo Dainippon. ST reports grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan, the Ministry of Health, Welfare and Labour of Japan, and Japan Agency for Medical Research and Development. ST also reports personal fees from Mitsubishi Tanabe. YI reports grants from Health and Labour Sciences Research Grant, and personal fees from Mitsubishi Tanabe. GS reports grants from the Ministry of Health Labor and Welfare of Japan, the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the Japan Society for the Promotion of Science. GS also reports personal fees from Mitsubishi Tanabe, Shionogi & Co, Bristol-Myers Squibb, Sumitomo Dainippon, Novartis, Bayer Yakuhin, Pfizer, Boehringer Ingelheim, Kissei, Janssen, Teijin, FP Pharmaceutical Corporation, Nihon, Japan Blood Products, Kowa, Ono, Otsuka, and Eisai. CH reports personal fees from Mitsubishi Tanabe. MTo, MTa, MAk, KN, FT, and KK are employees of Mitsubishi Tanabe. HY reports personal fees from Mitsubishi Tanabe.

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