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CADTH COMMON DRUG REVIEW

Clinical Review Report

EDARAVONE (RADICAVA)

(Mitsubishi Tanabe Pharma Corporation)

Indication: For the treatment of amyotrophic lateral sclerosis

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

FVC	forced vital capacity
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSAQ-40	40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised
BiPAP	bilevel positive airway pressure
CI	confidence interval
ED	edaravone
FVC	forced vital capacity
HRQoL	health-related quality of life
LMN	lower motor neuron
LOCF	last observation carried forward
LSM	least squares mean
LTSE	long-term safety extension
MCID	minimum clinically important difference
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
UMN	upper motor neuron
WDAE	withdrawal due to adverse event

Drug	Edaravone (Radicava)
Indication	For the treatment of amyotrophic lateral sclerosis (ALS)
Reimbursement Request	As per indication
Dosage Form(s)	Intravenous solution, 30 mg/100 mL per infusion bag
NOC Date	October 3, 2018
Manufacturer	Mitsubishi Tanabe Pharma Corporation

Executive Summary

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disorder that is characterized by the degeneration of upper and lower motor neurons. Symptoms of ALS are typically first noticed when limb weakness occurs, though the first symptoms can also be bulbar and involve difficulty in speaking or swallowing. Over time, patients lose function in additional regions, such as the other limbs and respiratory muscles. Progressive muscle weakness and eventual respiratory failure lead to death. Patients are typically in their middle to late 50s when they present with symptoms,[1] and median survival time from onset to death estimated from population-based studies ranges from 20 to 36 months.[2] The etiology of the disease is unknown and at least 25 genes have been reproducibly shown to be associated with ALS.[1] There is no definitive test for diagnosing ALS and there is typically a long duration from symptom onset to diagnosis. Diagnosis is based on clinical examination, electrophysiology tests, and exclusion of mimics.[3] Canadian estimates of annual incidence of ALS have ranged from 2.0 to 2.3 per 100,000 persons for age-adjusted incidence[4] and from 2.4 to 3.3 per 100,000 persons for crude incidence.[5,6]

There is no cure for ALS and the only approved disease-modifying treatment for ALS is the oral drug riluzole, which has been shown to extend tracheostomy-free survival by two to three months.[7] Medication can also be used to treat ALS symptoms, but can also cause other symptoms. Multidisciplinary non-pharmacologic care is important for managing symptoms and improving quality of life for patients with ALS. Multidisciplinary care optimally should involve a neurologist, gastroenterologist, respiratory physician, palliative care physician, and health care practitioners in the following areas: specialist nursing, physiotherapy, occupational therapy, nutrition, speech language pathology, and psychology.[8-10]

Edaravone (Radicava) is a free-radical scavenger thought to prevent oxidative damage to vascular endothelial cells and nerve cells. It is available as 30 mg edaravone in 100 mL isotonic, sterile, aqueous solution and is administered intravenously at 60 mg over a 60-minute period. The recommended treatment regimen starts with an initial treatment cycle of daily dosing for 14 days followed by a 14-day drug-free period. Subsequent treatment cycles involve daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. The Health Canada–approved indication under review is for the treatment of ALS.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of edaravone for the treatment of ALS.

Results and Interpretation

Included Studies

Four randomized trials were included in this review. Three of these were double-blind, parallel-group randomized controlled trials (RCTs) conducted in multiple centres in Japan in patients with ALS randomized (1:1) to edaravone or placebo: Study MCI186-16 (N = 206; referred to here as Study 16; conducted from 2006 to 2008), Study MCI186-18 (N = 25; referred to here as Study 18; conducted from 2006 to 2008), and Study MCI186-19 (N = 137; referred to here as Study 19; conducted from 2011 to 2014). The fourth RCT, Study MCI186-17 (N = 181; referred to here as Study 17; conducted from 2007 to 2009), was a parallel-group extension randomized trial in patients who had completed Study 16. Patients at the beginning of Study 16 were randomized (1:1:2) to edaravone in Study 16 and placebo in Study 17 (edaravone-placebo group), edaravone in Study 16 and edaravone in Study 17 (edaravone-edaravone group), or placebo in Study 16 and edaravone in Study 17 (placebo-edaravone group). Practically, this approach led to the allocation of patients on a 1:1 edaravone-to-placebo ratio in Study 16, and the allocation of patients on a 1:1:2 ratio of edaravone (from previous edaravone group), to placebo (from previous edaravone group), to edaravone (from previous placebo group) in Study 17. Studies 16, 18, and 19 had a 12-week screening period (referred to as the pre-observation period) prior to randomization. All four RCTs had a treatment period made up of six four-week treatment cycles for a total of 24 weeks of treatment following randomization.

Patients in Study 16 had to be categorized as either definite ALS, probable ALS, or "probable ALS – laboratory supported" according to the El Escorial revised Airlie House diagnostic criteria. They also had to have grade 1 or 2 ALS according to the Japanese ALS severity classification, have a forced vital capacity (FVC) of at least 70%, and be within three years of ALS onset. The inclusion criteria were the same in Study 18 as for Study 16, except that patients had to have grade 3 ALS according to the Japanese ALS severity classification and an FVC of at least 60%. Patients in Study 19 had to be categorized as definite ALS or probable ALS, have grade 1 or 2 ALS, have an FVC of at least 80%, be within two years of ALS onset, and score at least two points on the "handwriting" and "eating motion" items of the ALS Functional Rating Scale – Revised (ALSFRS-R). In studies 16, 18, and 19, patients had to have a decrease in ALSFRS-R score of one to four points during the 12-week pre-observation period prior to initiation of treatment. In all of these studies, the concomitant use of riluzole was allowed with no change in dose or administration route during the trials; however, riluzole therapy could not be initiated during the trials.

There were imbalances between treatment groups in each study regarding study discontinuations, with greater than 10% of patients discontinuing in some treatment groups. In studies 16 and 19, greater proportions of patients in the placebo groups discontinued, while the opposite was true in studies 17 and 18. The between-group difference was greatest in Study 17, with 15.6% in the edaravone-placebo group and 29.2% in the edaravone-edaravone group discontinuing. Given that last observation carried forward (LOCF) was used for missing data in patients who completed three treatment cycles and whose ALS was associated with a steady decline in motor function, the direction of potential

bias would have favoured the treatment group with the greater proportion of discontinuations (provided they occurred following the third treatment cycle).

The main two confirmatory trials (studies 16 and 19) restricted the patient population to patients who had a largely preserved respiratory function (Study 16 ≥ 70% FVC, and Study 19 ≥ 80% FVC) and functional independence. Study 18 was a small exploratory trial, which limits the generalizability of the results in the full patient population. All of the patients in the studies were Japanese; however, there does not seem to be any evidence suggesting that this, in and of itself, has an impact on the generalizability of the study findings to the ALS patient population in Canada.

Efficacy

The primary efficacy end point in studies 16, 17, and 19 was the change in ALSFRS-R total score from baseline to the end of treatment (end of cycle 6). Study 16 showed no statistically significant differences in ALSFRS-R score between the edaravone and placebo groups, with a reported change from baseline of −5.70 (standard error [SE] = 0.85) in the edaravone group compared with −6.35 (SE = 0.84) in the placebo group (least squares mean [LSM] difference = 0.65 [95% confidence interval [CI], −0.90 to 2.19]). Similarly, Study 17 showed no statistically significant difference in ALSFRS-R score between the edaravone-edaravone and edaravone-placebo groups, with a reported change from baseline of −4.42 (SE = 0.69) in the edaravone-edaravone group compared with −5.58 (SE = 0.74) in the edaravone-placebo group (LSM difference = 1.16 [95% CI, −0.70 to 3.01]). Similarly, Study 18 showed no statistically significant differences in its exploratory outcomes of ALSFRS-R score between the edaravone and placebo groups, with a reported change from baseline of −6.52 (SE = 1.78) in the edaravone group compared with −6.00 (SE = 1.83) in the placebo group (LSM difference = −0.52 [95% CI, −5.62 to 4.58]). However, Study 19 did show a statistically significant difference in the change from baseline between the edaravone (−5.01 [SE = 0.064]) and placebo groups (−7.5 [SE = 0.66]), with an LSM difference of 2.49 (95% CI, 0.99 to 3.98) in favour of edaravone. These results were supported by similar observations in the secondary outcome, the change in the Modified Norris Scale at the end of six treatment cycles. In addition, the Study 19 quality-of-life measure, the 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40), showed a nominal statistical significance favouring edaravone over placebo in total score, although a minimal clinically important difference (MCID) was not found for the ALSAQ-40 total score.

Survival analysis did not show any differences between treatment groups in death or certain disease-progression events in any of the RCTs. Pulmonary function assessed through FVC showed no statistically significant difference in any of the included studies. Similarly, no edaravone-favourable result was observed with regard to muscle strength or quality of life (outside Study 19).

Harms

Throughout the included studies, infections and infestations and gastrointestinal disorders were the most commonly reported adverse events (AEs). No notable harms related to the method of administration were considered serious, aside from one serious adverse event of catheter-site infection in the placebo-edaravone group of Study 17. AEs related to injection, infusion, or catheter site were each reported in less than 5% of each group in all the trials. However, the product monograph for edaravone notes hypersensitivity reactions and cases of anaphylaxis have been reported in spontaneous post-marketing reports on edaravone.

There was no clear congregation of a specific AE in the edaravone arm as opposed to the placebo arm. Serious AEs were seen but were related to the disease, while deaths were due mostly to respiratory-related events that are also commonly seen in patients suffering from ALS.

In Study 16, a lower percentage of patients in the edaravone group (2.9%) withdrew due to AEs than in the placebo group (7.7%). In Study 17, the edaravone-edaravone group had a higher percentage of withdrawals due to AEs (WDAEs) (18.8%) compared with the placebo-edaravone (9.1%) and the edaravone-placebo (6.7%) groups. In Study 18, a higher percentage of patients in the edaravone group withdrew due to AEs (7.7%) compared with the placebo group (0%). In Study 19, 2.9% of the patients in the placebo group withdrew due to AEs, while no WDAEs were reported in the edaravone group. Across studies 16, 17, and 18, respiratory failure was the most common AE that led to withdrawal.

There were five deaths reported in Study 16, two (1.9%) in the placebo group and three (2.9%) in the edaravone group. A further six deaths were reported in Study 17, including one (2.2%) in the edaravone-placebo group, and four (8.3%) in the edaravone-edaravone group. One death (7.7%) was reported in Study 18 in the edaravone group. No deaths were reported in Study 19. Respiratory failure and respiratory-related disorders were the cause of death in all cases except one, which was due to cardiac arrest.

Potential Place in Therapy[1]

Clinical experts consulted by CADTH stated that — given the natural history of ALS, a fatal disease — the unmet needs of ALS patients are colossal. Any drug that slows down disease progression would be welcome, as the benefit of riluzole is marginal, according to the clinical experts. Edaravone has demonstrated benefit in slowing disease progression in a randomized controlled phase III study (Study 19: 33% over six months) and should be considered for the majority of ALS patients with preserved respiratory function and with functional independence. Edaravone appears to be associated with few serious side effects, which also makes it attractive for widespread use in ALS.

The clinical experts noted that in order for Study 19 to show benefit in a short period of time (six months), very strict inclusion criteria were chosen, targeting ALS patients with a clear diagnosis, preserved respiratory function and functional independence, and an average rate of symptom worsening. Therefore, they excluded “possible ALS” patients (as per El Escorial criteria) to avoid misdiagnosis. Practically speaking, possible ALS likely represents the earliest stage of ALS for most patients; therefore, these patients should definitely be candidates for edaravone when diagnosed by ALS experts. Also, studies have shown that the vast majority of possible ALS patients develop definite ALS over time, and patients with possible ALS are included in most clinical trials. In addition, a drug like edaravone with a neuroprotective mechanism should be used as early as possible in a neurodegenerative disease like ALS.

To enter the study, patients had to show a decline in their ALSFRS score of one to four points in a three-month observation period. This observation period cannot be replicated in real-life situations and would likely be unethical, as a neuroprotective drug is most beneficial early in the disease course.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Inclusion criteria also included an FVC above 80% without respiratory complaints. Other criteria targeted early-disease patients: less than two years since ALS onset, grade 1 or 2 ALS according to the Japanese severity scale, and a score above 1 on each item of the ALSFRS-R scale.

While the majority of newly diagnosed ALS patients will meet these criteria, early diagnosis is not always possible, as no biomarker exists for ALS; the diagnosis relies on clinical examination and electromyography (EMG) and the exclusion of other entities, which often delays diagnosis. In that context, patients diagnosed later would likely also benefit from the drug based on its presumed effects on the pathophysiology of ALS, although these patients were excluded from Study 19 because of the strict inclusion criteria.

In practice, edaravone should be offered to almost all newly diagnosed ALS patients. Its mode of administration — intravenous infusions for 10 to 14 days per month — is the main barrier for widespread use. Some patients may refuse this invasive therapy or be unable to travel to obtain it if the drug cannot be infused at home. Patients with advanced ALS with severe disability, such as ventilator-dependent patients with very little limb function, are unlikely to benefit from therapy and should not be offered edaravone.

Most patients with ALS who do not fulfill the strict inclusion criteria of Study 19 would likely benefit from the drug early in their disease course based on its presumed mode of action and should be offered the treatment.

Evidence is lacking for several groups of patients, such as those who progress more slowly over several years, or patients with concomitant frontotemporal dementia. A decision on treatment for these groups should therefore be weighed by the clinician after discussion with the patient and family members, acknowledging lack of data in these circumstances.

Conclusions

Four RCTs evaluating the efficacy and safety of edaravone versus placebo in patients with ALS were included in this CADTH Common Drug Review (CDR) systematic review. Two RCTs (Study 16 and Study 19) were confirmatory trials, while one was an extension of Study 16 (Study 17) and one was an exploratory trial (Study 18). Study 19 demonstrated a statistically significant and clinically meaningful decreased rate of decline in the edaravone group compared with the placebo group, as measured using the ALSFRS-R change from baseline. This result was further supported by nominal statistically significant findings in the secondary outcomes: change in the Modified Norris Scale from baseline and change in health-related quality of life using the ALSAQ-40. Other outcomes related to respiratory function, strength, and disease severity classification did not show between-group differences. No statistically significant finding was demonstrated in other studies. Throughout the included studies, no specific AE was markedly more concentrated in the edaravone group than in the placebo group, and all causes of death and serious AEs can be common manifestations of ALS. Hypersensitivity reactions and cases of anaphylaxis have been reported in spontaneous post-marketing reports on edaravone. However, these reactions were not observed in the included studies.

While edaravone demonstrated efficacy in decreasing the decline of motor function in patients included in Study 19, its effect on survival, respiratory function, and quality of life are unclear. Patients in Study 19 had baseline disease characteristics corresponding to the early stages of ALS and the extent of the effectiveness of edaravone on patients at later stages of the disease is also unclear. Study 16 showed a decreased rate of decline in the

ALSFRS-R score in the edaravone group versus the placebo group, but the difference was not statistically significant. The lack of statistical significance for the treatment effect may have been due to the broader range in disease characteristics in the Study 16 patients as opposed to a lack of true efficacy, though the evidence is not conclusive.

Table 1: Summary of Results

	Study 16 FAS		Study 17 FAS		Study 18		Study 19 FAS	
Survival analysis for Death or certain disease progression	**PL N = 104**	**ED N = 101**	**ED-PL N = 44**	**ED-ED N = 48**	**PL N = 12**	**ED N = 13**	**PL N = 68**	**ED N = 69**
Total, N (%)	37 (35.6)	38 (37.6)	13 (29.5)	19 (39.6)	4 (33.3)	7 (53.8)	6 (8.8)	2 (2.9)
Death	2 (1.9)	2 (2.0)	1 (2.3)	1 (2.1)	0	1 (7.7)	0	0
P value	NR		NR		NR		0.1415	
Assessment of motor function using ALSFRS-R score (primary outcome)	**PL N = 99**	**ED N = 100**	**ED-PL N = 41**	**ED-ED N = 45**	**PL N = 12**	**ED N = 13**	**PL N = 66**	**ED N = 68**
Baseline, mean (SD)	41.2 (2.9)	40.6 (3.5)	36.5 (5.5)	36.0 (6.1)	34.6 (3.3)	32.5 (5.5)	41.8 (2.2)	41.9 (2.4)
End point, mean (SD)	35.1 (7.4)	35.3 (7.1)	31.5 (7.7)	32.3 (8.1)	29.2 (4.9)	26.6 (9.9)	35.0 (5.6)	37.5 (5.3)
Change from baseline, LS mean (SE)	−6.35 (0.84)	−5.70 (0.85)	−5.58 (0.74)	−4.42 (0.69)	−6.00 (1.83)	−6.52 (1.78)	−7.5 (0.66)	−5.01 (0.64)
Between-group difference, LS mean (95% CI)	0.65 (−0.90 to 2.19)		1.16 (−0.70, 3.01)		−0.52 (−5.62 to 4.58)		**2.49 (0.99 to 3.98)**	
P value	0.4108		0.2176		0.8347		**0.0013**	
Assessment of motor function using Modified Norris Scale score (total score)	**PL N = 97**	**ED N = 95**	**ED-PL N = 41**	**ED-ED N = 44**	**PL N = 12**	**ED N = 12**	**PL N = 63**	**ED N = 68**
Baseline, mean (SD)	86.9 (9.6)	84.6 (11.1)	74.8 (17.2)	73.3 (16.3)	69.5 (13.2)	63.8 (18.6)	88.0 (6.7)	87.9 (7.8)
End point, mean (SD)	71.7 (19.3)	72.3 (18.9)	62.6 (21.8)	63.7 (20.1)	53.1 (15.0)	49.3 (25.9)	70.5 (16.7)	75.2 (15.4)
Change from baseline, LS mean (SE)	−16.15 (2.00)	−14.12 (2.05)	−14.02 (1.76)	−10.84 (1.68)	−17.76 (3.80)	−18.18 (3.80)	−20.8 (2.06)	−15.9 (1.97)
Between-group difference, LS mean (95% CI)	2.03 (−1.69 to 5.75)		3.19 (−1.32 to 7.69)		−0.42 (−11.27 to 10.44)		**4.89 (0.24 to 9.54)**	
P value	0.2835		0.1634		0.9371		**0.0393**	
Assessment of respiratory function using FVC	**PL N = 99**	**ED N = 100**	**ED-PL N = 41**	**ED-ED N = 44**	**PL N = 12**	**ED N = 12**	**PL N = 66**	**ED N = 68**
Baseline, mean (SD)	95.78 (17.04)	95.53 (14.97)	88.18 (20.75)	84.52 (24.57)	86.48 (16.5)	83.9 (23.5)	97.4 (13.6)	100.5 (15.0)
End point, mean (SD)	80.12 (23.16)	83.11 (25.26)	80.08 (25.73)	75.46 (26.16)	71.47 (23.0)	62.6 (36.2)	80.5 (24.0)	87.6 (24.0)
Change from baseline, LS mean (SE)	−17.49 (2.39)	−14.57 (2.41)	−10.15 (2.44)	−13.33 (2.29)	−15.69 (4.58)	−18.75 (4.58)	−20.4 (2.48)	−15.6 (2.41)
Between-group difference, LS mean (95% CI)	2.92 (−1.49 to 7.33)		−3.17 (−9.32 to 2.97)		−3.06 (−16.12 to 10.00)		4.78 (−0.83 to 10.40)	
P value	0.1928		0.3074		0.6313		0.0942	

	Study 16 FAS		Study 17 FAS		Study 18		Study 19 FAS	
Assessment of patients' health-related quality of life using ALSAQ-40	**PL N = 95**	**ED N = 95**	**ED-PL N = 41**	**ED-ED N = 44**	**PL N = 12**	**ED N = 11**	**PL N = 64**	**ED N = 68**
Baseline, mean (SD)	92.5 (22.6)	97.6 (23.4)	110.2 (28.4)	118.3 (33.2)	112.1 (22.3)	122.2 (33.7)	91.4 (19.3)	89.1 (21.2)
End point, mean (SD)	110.9 (31.8)	116.2 (33.1)	125.6 (31.9)	128.7 (31.4)	137.1 (28.4)	139.6 (27.0)	117.2 (26.7)	105.7 (26.2)
Change from baseline, LS mean (SE)	19.13 (3.79)	19.60 (3.82)	18.99 (3.03)	13.54 (2.89)	26.33 (5.34)	20.91 (5.71)	26.0 (3.53)	17.2 (3.39)
Between-group difference, LS mean (95% CI)	0.48 (−6.44 to 7.39)		−5.45 (−13.19 to 2.29)		−5.42 (−21.05 to 10.20)		−8.79 (−16.76 to −0.82)	
P value	0.8921		0.1651		0.4773		**0.0309**	
Discontinuation								
Total, N (%)	14 (13.5)	9 (8.8)	7 (15.6)	14 (29.2)	0	4 (30.8)	8 (11.8)	2 (2.9)
SAEs								
Total, N (%)	24 (23.1)	18 (17.6)	13 (28.9)	25 (52.1)	2 (16.7)	3 (23.1)	16 (23.5)	11 (15.9)
WDAEs								
Total, N (%)	8 (7.7)	3 (2.9)	3 (6.7)	9 (18.8)	0	1 (7.7)	2 (2.9)	0
Deaths								
Total, N	2	3	1	4	0	1	0	0

AE = adverse event; ALS = amyotrophic lateral sclerosis; ALSAQ-40 = 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; CI = confidence interval; ED = edaravone; FAS = full analysis set; LS = least squares; NR = not reported; PL = placebo; SAE = serious adverse event; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

Note: Efficacy data are reported for the period from the start of cycle 1 to the end of cycle 6 for studies 16, 18, and 19 and the period from the start of cycle 7 to the end of cycle 12 for Study 17.

Note: ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17.

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] MCI186-18,[13] and MCI186-19.[14]

Introduction

Disease Background

Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disorder that is characterized by the degeneration of upper and lower motor neurons. Symptoms of ALS are typically first noticed when limb weakness occurs, though the first symptoms can also be bulbar and involve difficulty in speaking or swallowing. Over time, patients lose function in additional regions, such as the other limbs and respiratory muscles. Progressive muscle weakness and eventual respiratory failure lead to death. Patients are typically in their middle to late 50s when they present with symptoms[1] and median survival time from onset to death estimated from population-based studies ranges from 20 to 36 months.[2] ALS is a clinically heterogeneous disease in terms of presentation and rate of progression. For example, 5% to 10% of patients with ALS survive past 10 years from onset.[2] Approximately 10% of ALS cases are familial ALS, which is associated with an earlier onset. The etiology of the disease is unknown and at least 25 genes have been reproducibly shown to be associated with ALS.[1]

There is no definitive test for diagnosing ALS and there is typically a long duration from symptom onset to diagnosis. According to the clinical experts consulted by the CADTH Common Drug Review (CDR) for this review, patients present with a localized symptom, such as limb weakness or change in voice, and rarely feel unwell. The disease is heterogeneous and diagnosis is based on clinical examination, electrophysiology tests, and exclusion of mimics. The lack of a useful ALS biomarker contributes to delays in diagnosis and difficulty in monitoring disease progression or activity in response to treatment.[15] Expert consensus on diagnostic criteria was established in 1994 with the El Escorial criteria and a subsequent version was established in 1999 as the El Escorial revised Airlie House criteria.[16] The criteria have been used mainly for standardizing clinical trials as opposed to diagnosing patients in clinical practice.[16] In the revised criteria, patients are categorized as having clinically definite ALS, probable ALS, "probable ALS – laboratory supported," or possible ALS. The criteria are based on the presence of upper motor neuron (UMN) or lower motor neuron (LMN) signs in the following four regions of involvement: the brainstem and the cervical, thoracic, and lumbosacral spinal cord. The categories and criteria are as follows:[17]

- definite ALS: Clinical UMN and LMN signs in three regions of involvement
- probable ALS: Clinical UMN and LMN signs in at least two regions, with some UMN signs rostral to the LMN signs
- probable ALS – laboratory supported: Clinical UMN and LMN signs in one region or UMN signs in one region accompanied by electrophysiological signs in at least two regions
- possible ALS: Clinical UMN and LMN signs in one region, UMN signs in two or more regions alone, or LMN signs found rostral to UMN signs (without proof of "probable ALS – laboratory supported").

With these criteria, the sensitivity of the categories (definite ALS, probable ALS, and "probable ALS – laboratory supported") combined for identifying patients with ALS was estimated to be 62.2% (95% confidence interval [CI], 49.4% to 75.1%) in a meta-analysis.[18] The corresponding specificity was estimated to be 98.2% (95% CI, 96.7% to 99.7%).[18] Prior to 2010, most clinical trials enrolled only patients who met the criteria for these three

categories.[16] More recently, it has been proposed that patients with possible ALS could also be enrolled in clinical trials and that information from other investigations, such as magnetic resonance imaging and cerebral spinal fluid examinations, may help with the differential diagnosis.[19]

Patient input provided to CDR indicated that nearly all patients surveyed or interviewed reported decreased muscle tone and muscle fatigue, discomfort, stiffness, cramps, and twitches. This imposes a challenge on many tasks that are performed on a daily basis. As motor function is lost, reduced mobility contributes to joint discomfort and stiffness, as well as issues with circulation, which leads to swollen legs and feet. Assistance is often required for everyday tasks such as walking, transitions from sitting to standing and transitions from lying to sitting. Another common consequence of the disease is the patient's loss of bladder or bowel control. The need for assistance is quite demanding for caregivers who also report having to plan their day around being able to provide that support. As the disease progresses, patients experience issues with breathing as a result of cramping or weakness of the diaphragm. Patients also experience difficulty eating and drinking as well as communicating through speech, typing, or writing; patients report these difficulties have an isolating effect. As a result of the various, debilitating ways ALS affects one's life, the disease impacts the mental health of some patients. Patients reported apathy or depressive behaviour, difficulty controlling their emotions at times, inattention, obsessive or unusual behaviour, and mood changes or frontotemporal dementia symptoms. The mental health of caregivers is affected as well, as caregivers witness their loved ones progress through the disease. The patient input also noted that ALS poses a financial burden, which includes purchasing medical equipment, making home modifications, transporting the patient to appointments, and affects patients' and caregivers' ability to work.

The estimated survival from time of ALS onset to death varies between studies. According to a systematic review that summarized factors that may have an impact on survival,[2] increasing age of symptom onset, bulbar onset ALS, faster rate of decline in functional measures, poor nutritional status, reduced respiratory function, and a diagnosis of "definite ALS" have been shown to be associated with shorter survival.[2] The use of a gastrostomy feeding tube may improve survival,[2] and the use of non-invasive ventilation has been shown in controlled trials to prolong survival.[20]

Disease progression can be described using one of the clinical staging systems, three of which are described here. The King's clinical staging system consists of the following stages based on regions of involvement: involvement of first region (stage 1), involvement of second region (stage 2), involvement of third region (stage 3), need for gastrostomy (stage 4A), and need for non-invasive ventilation (stage 4B).[21] A more recent system, the Milano-Torino functional staging system, consists of the following stages, which are based on loss of independence: functional involvement without loss of independence (stage 0), loss of independence in one to four domains (stages 1 to 4), and death (stage 5).[22] The Japanese ALS severity classification, which was used in the development of edaravone, consists of the following stages based on functional ability: able to work or perform housework (stage 1), independent living but unable to work (stage 2), requiring assistance for eating, excretion, or ambulation (stage 3), presence of respiratory insufficiency, difficulty in coughing out sputum or dysphagia (stage 4), and using a tracheostomy tube, tube feeding, or tracheostomy positive-pressure ventilation (stage 5).[23]

Disease Incidence

A systematic review published in 2009[4] summarized the results from five studies reporting the incidence of ALS in three Canadian provinces, with three studies in Nova Scotia, one in Ontario, and one in Newfoundland and Labrador. Estimates of age-adjusted annual incidence per 100,000 persons ranged from 2.0 to 2.3 in four studies, with the fifth study estimating a crude annual incidence rate of 2.4 per 100,000 persons in Newfoundland and Labrador. Since the 2009 systematic review, one study of incident cases from 2010 to 2015 in British Columbia estimated a crude annual incidence rate of 3.29 per 100,000 persons,[5] and one study in the region of Saguenay–Lac-Saint-Jean in Québec found an annual crude incidence of 3.01 per 100,000 persons during the period from 2005 to 2009.[6] A systematic review[24] of incidence rates of ALS worldwide found a crude incidence rate overall of 1.75 per 100,000 person-years of follow-up (95% CI, 1.55 to 1.96) with region-specific values ranging from 0.43 in Iran to 2.35 per 100,000 in western Europe.

Standards of Therapy

There is no cure for ALS and the only disease-modifying treatment available is the oral drug riluzole. According to the clinical experts consulted for this review, most patients with ALS in Canada receive riluzole, which has been shown to extend tracheostomy-free survival by two to three months.[7] About half of the respondents in the patient input provided to CDR reported using riluzole and perceived efficacy of riluzole was mixed. Riluzole is contraindicated for patients with hepatic disease or elevated liver enzymes. Adverse events (AEs) reported by patient respondents included cramps, diarrhea, heartburn, and feeling sick. ALS symptoms may be managed (to varying degrees) by a range of pharmacologic therapies, including antidepressants, anti-anxiety and sleeping medications, muscle relaxants and antispasmodics, medications to manage sialorrhea, and medications to address gastrointestinal upset. These drugs, however, are associated with a wide range of AEs; with the use of multiple medications, patients also reported experiencing sleepiness, diarrhea, constipation, fatigue, and mood changes, which impacts their ability to function.

Multidisciplinary non-pharmacologic care is important for managing symptoms and improving quality of life for patients with ALS. Multidisciplinary care optimally should involve a neurologist, gastroenterologist, respiratory physician, and palliative care physician as well as health care practitioners in the following areas: specialist nursing, physiotherapy, occupational therapy, nutrition, speech language pathology, and psychology.[8-10] However, only approximately half of patient respondents who provided input to CDR reported having access to a multidisciplinary care clinic, and there were difficulties reported in travelling to clinics and delays in accessing equipment and devices, allied health services, and home care, and limitations to government-funded programs were identified. The patient group input provided to CDR indicated that patients use a wide range of assistive devices, from wheelchairs to a bilevel positive airway pressure (BiPAP) machine for non-invasive ventilation to assist with challenges associated with mobility and activities of daily living. In Canadian clinics, the decision to introduce non-invasive ventilation is mostly based on patient symptoms (dyspnea, orthopnea, and morning headache), nocturnal oximetry, and forced vital capacity (FVC), and a survey published in 2010 found that 18.3% of Canadian patients with ALS were using non-invasive ventilation.[25] Patient intolerance and lack of access to a respirologist or ventilation technologist were identified as the most common barriers to utilization.[25] As a second-line respiratory intervention, the use of invasive ventilation with a tracheostomy is associated with high cost and emotional and social

impacts and the Canadian survey found that 1.5% of patients with ALS were using invasive ventilation, a proportion similar to that of patients in the US (2.1% to 4%) and Europe (1% to 31%), and lower than in Japan (29% to 38%).[25,26] The insertion of a gastrostomy feeding tube is recommended in US[27] and European[8] guidelines to supplement nutrition and stabilize weight loss. Decline in respiratory function, dysphagia, and weight loss factor into the decision to place a feeding tube, though decision-making criteria vary between Canadian clinics.[28]

Drug

Edaravone (Radicava) is a free-radical scavenger thought to prevent oxidative damage to vascular endothelial cells and nerve cells. It is available as 30 mg edaravone in a 100 mL isotonic, sterile, aqueous solution and is administered intravenously over a 60-minute period. The recommended treatment regimen starts with an initial treatment cycle of daily dosing for 14 days followed by a 14-day drug-free period. Subsequent treatment cycles involve daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. Edaravone is indicated for the treatment of ALS.

Table 2: Key Characteristics of Edaravone and Riluzole

	Edaravone	Riluzole
Mechanism of Action	The mechanism by which edaravone exerts its therapeutic effect in patients with ALS is unknown	The mode of action of riluzole is unknown, though its pharmacological properties include the following: • an inhibitory effect on glutamate release • inactivation of voltage-dependent sodium channels • ability to interfere with intracellular events that follow transmitter binding to excitatory amino acid receptor
Indication[a]	Treatment of amyotrophic lateral sclerosis	May extend survival and/or time to tracheostomy in some patients with ALS
Route of Administration	Intravenous	Oral
Recommended Dose	60 mg administered over a 60-minute period, according to the following schedule: • an initial treatment cycle with daily dosing for 14 days followed by a 14-day drug-free period • subsequent treatment cycles with daily dosing for 10 days out of a 14-day period followed by 14-day drug-free periods	One 50 mg tablet every 12 hours
Serious Side Effects / Safety Issues	Hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous post-marketing reports	Riluzole is contraindicated in patients who have hepatic disease or who have baseline transaminases > 3 × upper limit of normal

ALS = amyotrophic lateral sclerosis.

[a] Health Canada indication.

Source: Product monographs for Radicava[29] and Rilutek.[30]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of edaravone intravenous solution, 30 mg/100 mL per infusion bag, administered as an intravenous infusion of 60 mg over a 60-minute period as two consecutive 30 mg/100 mL infusion bags over an initial cycle of daily doses for 14 days followed by a 14-day drug-free period and subsequent cycles of daily doses for 10 days out of a 14-day period, followed by a 14-day drug-free period, for the treatment of ALS.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Patients with ALS diagnosis **Subgroups:** • time since symptoms onset until initiation of edaravone • ALS severity grades • family history (familial ALS) • site of onset
Intervention	Edaravone intravenous solution, 30 mg/100 mL per infusion bag, administered as an intravenous infusion of 60 mg over a 60-minute period as two consecutive 30 mg/100 mL infusion bags over an initial cycle of daily doses for 14 days followed by a 14-day drug-free period, and subsequent cycles of daily doses for 10 days out of a 14-day period; followed by a 14-day drug-free period ± standard of care
Comparators	• Riluzole ± standard of care • Placebo ± standard of care
Outcomes	**Efficacy outcomes:** • overall survival • assessment of motor function using a validated scale,[a] including: mobility, muscle strength, and use of feeding tube • assessment of respiratory function,[a] including forced vital capacity percentage, use of respirator, use of tracheostomy, and tracheostomy-free survival • assessment of patients' health-related QoL using a validated scale[a] • caregiver burden[a] • hospitalization **Harms outcomes:** • AEs, SAEs, WDAEs, mortality • AEs of special interest: skin and subcutaneous-tissue disorders, anaphylaxis, and complications due to insertion and use of central line
Study Design	Published and unpublished phase III and phase IV RCTs

AE = adverse event; ALS = amyotrophic lateral sclerosis; QoL=quality of life; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy (Appendix 2).

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

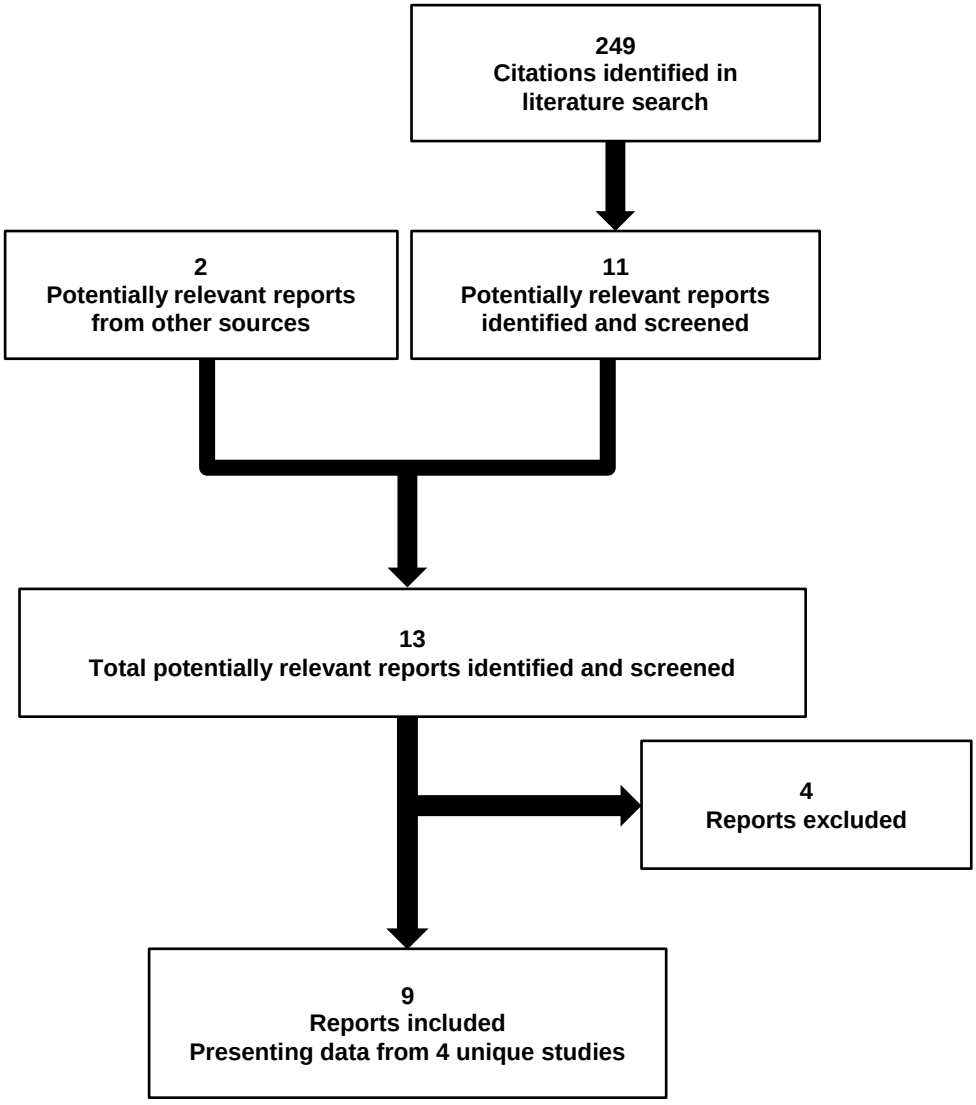

Table 4: Details of Included Studies

		Study 16 (MCI186-16)	Study 17 (MCI186-17)	Study 18 (MCI186-18)	Study 19 (MCI186-19)
Designs & Populations	**Study Design**	Phase III, DB, parallel-group RCT	Extension phase III study, two arms DB, one arm OL, RCT	Phase III, DB, parallel-group RCT	Phase III, DB, parallel-group RCT
	Locations	Japan	Japan	Japan	Japan
	Randomized (N)	206 (one excluded from FAS)	206 randomized, 181 participated	25	137
	Inclusion Criteria	At enrolment: • definite ALS, probably ALS, or "probable ALS –laboratory supported" according to the El Escorial revised Airlie House diagnostic criteria • grade 1 or 2 ALS according to the Japanese ALS severity classification • FVC of ≥ 70% • ≤ 3 years since onset of ALS • age of 20 to 75 years At randomization: • a change in ALSFRS-R score of −1 to −4 points during the 12-week pre-observation period	Completion of Study 16	At enrolment: • definite ALS, probably ALS, or "probable ALS – laboratory supported" according to the El Escorial revised Airlie House diagnostic criteria • grade 3 ALS according to the Japanese ALS severity classification • FVC of ≥ 60% • ≤ 3 years since onset of ALS • age of 20 to 75 years At randomization: • a change in ALSFRS-R score of −1 to −4 points during the 12-week pre-observation period	At enrolment: • definite ALS or probable ALS according to the El Escorial revised Airlie House diagnostic criteria • grade 1 or 2 ALS according to the Japanese ALS severity classification • score of ≥ 2 points on each item of the ALSFRS-R (on each side for "handwriting" and "eating motion") • FVC of ≥ 80% (using actual values) • ≤ 2 years since onset of ALS • age of 20 to 75 years At randomization: • a change in ALSFRS-R score of −1 to −4 points during the 12-week pre-observation period
	Exclusion Criteria	• Comorbidities that could affect efficacy evaluation (e.g., Parkinson's disease, schizophrenia, or dementia) • Renal impairment in the 28 days prior to the start of treatment • Judged by the investigator to be ineligible due to general condition deterioration due to complications requiring hospitalization or concomitant infections requiring antibiotic treatment • History of hypersensitivity to edaravone • Participation in another clinical study within 12 weeks of enrolment • Otherwise judged by the investigator to be ineligible		• Decreased respiratory function and a complaint of dyspnea (≤ 3 points on any of the following ALSFRS-R items under "respiration": dyspnea, orthopnea, or respiratory insufficiency • Comorbidities that could affect efficacy evaluation (e.g., Parkinson's disease, schizophrenia, or dementia) • Renal impairment in the 28 days prior to the start of treatment • Otherwise judged by the investigator to be ineligible	
		• Decreased respiratory function	• Undergoing treatment for a concomitant	• Judged by the investigator to be	• History of spinal surgery after ALS

		Study 16 (MCI186-16)	Study 17 (MCI186-17)	Study 18 (MCI186-18)	Study 19 (MCI186-19)
		and a complaint of dyspnea (≤ 3 points on any of the following ALSFRS-R items under "respiration": dyspnea, orthopnea, or respiratory insufficiency • History of treatment for malignancy	malignancy	ineligible due to general condition deterioration due to complications requiring hospitalization or concomitant infections requiring antibiotic treatment • History of treatment for malignancy • History of hypersensitivity to edaravone	onset or plans for spinal surgery during the study period • Current symptoms may be of a disease requiring differential diagnosis (e.g., cervical spondylosis, multifocal motor neuropathy) • Treatment for concomitant malignancy • Previously administered edaravone • Significant complication (grade 3 adverse drug reaction used as reference) • Administered an investigative product within 12 weeks of enrolment
DRUGS	**Intervention**	• 60 mg edaravone diluted in saline-infused IV over 60 minutes once daily • Treatment cycle 1: Administered for 14 consecutive days followed by a 2-week drug-free period • Treatment cycles 2 to 6: Administered for a total of 10 days in a 2-week period followed by a 2-week drug-free period • Treatment cycles 7 to 15 (Study 17 only): Administered for a total of 10 days in a 2-week period, followed by a 2-week drug-free period			
	Comparator(s)	Placebo			
DURATION	**Phase**				
	Pre-observation	12 weeks	NA	12 weeks	
	Double-blind	24 weeks	24 weeks	24 weeks	
	Follow-up	See Study 17	12 weeks	NA	See Appendix 5
OUTCOMES	**Primary End Point**	Change in ALSFRS-R score from baseline in treatment cycle 1 to end of treatment cycle 6	Change in ALSFRS-R score from baseline in treatment cycle 7 to end of treatment cycle 12	Change in ALSFRS-R score from baseline in treatment cycle 1 to end of treatment cycle 6 (considered exploratory in Study 18)	
	Other End Points	• Time to death or disease progression (includes loss of independent ambulation, loss of upper-arm function, tracheotomy, use of respirator [not including BiPAP], use of tube feeding, and loss of useful speech [Study 19 only]) • Domain score of the ALSFRS-R (bulbar, limb, and respiratory) • FVC • Modified Norris Scale score and domain scores (limb and bulbar) • ALSAQ-40 • Grip strength • Pinch-grip strength • Japanese ALS severity classification • AEs, serious AEs, death			

		Study 16 (MCI186-16)	Study 17 (MCI186-17)	Study 18 (MCI186-18)	Study 19 (MCI186-19)
NOTES	**Publications**	Abe 2014[31] Edaravone ALS 16 Study Group 2017[32] Kalin 2017[33]	Edaravone ALS 17 Study Group 2017[34]	Edaravone ALS 18 Study Group[35]	Takei 2017[36] Edaravone ALS Study Group 2017[37]

AE = adverse event; ALS = amyotrophic lateral sclerosis; ALSAQ-40 = 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R = Amyotrophic Lateral Sclerosis Function Rating Scale – Revised; BiPAP = bilevel positive airway pressure; DB = double-blind; FAS = full analysis set; FVC = functional vital capacity; IV = intravenous; NA = not applicable; OL = open-label; RCT = randomized controlled trial.

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] MCI186-18,[13] and MCI186-19.[14]

Included Studies

Description of Studies

Details of the included studies are provided in Table 4. Four placebo-controlled, multi-centre RCTs met the selection criteria for the CDR systematic review:

- Three double-blind, parallel-group RCTs in patients with ALS were included. Patients were randomized (1:1) to edaravone or placebo: Study MCI186-16 (N = 206; referred to here as Study 16; conducted from 2006 to 2008), Study MCI186-18 (N = 25; referred to here as Study 18; conducted from 2006 to 2008), and Study MCI186-19 (N = 137; referred to here as Study 19; conducted from 2011 to 2014). The objective of these RCTs was to confirm (Study 16), explore (Study 18), or investigate (Study 19) the efficacy of edaravone versus placebo in patients with ALS (specifically patients with grade 3 ALS according to the Japanese ALS severity classification defined in Study 18) and examine the safety of edaravone in patients with ALS.
- Study MCI186-17 (N = 181; referred to here as Study 17; conducted from 2007 to 2009), was a parallel-group extension RCT in patients who had completed Study 16. Patients at the beginning of Study 16 were randomized (1:1:2) to edaravone in Study 16 and placebo in Study 17 (edaravone-placebo group), edaravone in Study 16 and edaravone in Study 17 (edaravone-edaravone group), or placebo in Study 16 and edaravone in Study 17 (placebo-edaravone group). The objective of Study 17 was to investigate the sustainability of the effects of edaravone and its long-term efficacy and safety as well as to collect information on when edaravone administration is resumed following placebo administration.

Following what was referred to as pre-registration, studies 16, 18, and 19 had a 12-week screening period (referred to as the pre-observation period) prior to randomization, and a subsequent 24-week treatment period. A non-randomized extension to Study 19 was also conducted and is summarized in Appendix 5.

Populations

Inclusion and Exclusion Criteria

Details on inclusion and exclusion criteria are provided in Table 4. Patients in Study 16 had to be categorized as definite ALS, probable ALS, or “probable ALS – laboratory supported” according to the El Escorial revised Airlie House diagnostic criteria, have grade 1 or 2 ALS according to the Japanese ALS severity classification, have an FVC of at least 70%, and be within three years of ALS onset. The inclusion criteria were the same in Study 18 as for Study 16, except that patients had to have grade 3 ALS according to the Japanese ALS

severity classification and an FVC of at least 60%. Patients in Study 19 had to be categorized as definite ALS or probable ALS, have grade 1 or 2 ALS, have an FVC of at least 80%, be within two years of ALS onset, and score at least two points on the "handwriting" and "eating motion" items of the ALS Functional Rating Scale – Revised (ALSFRS-R). In studies 16, 18, and 19, patients had to have a decrease in ALSFRS-R score of one to four points during the 12-week pre-observation period prior to initiation of treatment. Patients had to have completed Study 16 to participate in Study 17, an extension study.

Patients were excluded from Study 16, 18, and 19 if they had decreased respiratory function and a complaint of dyspnea according to the ALSFRS-R "respiration" items. In all four RCTs, patients were excluded if they had participated in a clinical study within 12 weeks of enrolment, had a complication that could affect efficacy evaluation, had renal impairment in the 28 days prior to the start of treatment, or were otherwise judged by the investigator to be ineligible. Patients in studies 16, 17, and 18 were excluded if they were judged to be ineligible due to deterioration in general condition from complications requiring hospitalization or concomitant infections requiring antibiotic treatment. Patients were excluded from Study 19 if they had a history of spinal surgery after onset of ALS or plans for spinal surgery during the study, or if they had symptoms of a disease requiring differential diagnosis.

Of note, the inclusion criteria in Study 19 were informed by post hoc analyses of Study 16, which suggested efficacy of edaravone in a subgroup of patients.

Baseline Characteristics

Baseline characteristics are provided in detail in Table 5. The patient populations in all four RCTs were similar among many demographic and baseline characteristics. Generally, most patients in each treatment group in each study were male, had an initial symptom classification of limb, had sporadic ALS, were categorized as "probable ALS" according to the El Escorial diagnostic criteria, had grade 2 ALS according to the Japanese ALS severity classification, and were taking riluzole in addition to another medication. Mean age ranged from 55.5 years to 60.1 years.

Patients in Study 19 had a mean age of 60.1 to 60.5 years compared with a mean age of 57.7 to 57.9 years in Study 16. Mean disease duration was 1.06 years to 1.13 years in Study 19, 1.30 years to 1.44 years in Study 16, and 1.75 years to 2.05 years in Study 18. The proportion of patients whose initial ALS symptoms were bulbar as opposed to limb was 17.8% to 19.2% in Study 16 and 20.6% to 23.3% in Study 19. Greater proportions of patients had grade 2 ALS as opposed to grade 1 ALS in Study 19 (68.1% to 76.5%) than in Study 16 (61.5% to 64.4%). The ALSFRS-R score at baseline was similar in studies 16 and 19, with mean scores ranging from 40.6 to 41.9. In contrast, the mean ALSFRS-R score at baseline in studies 17 and 18 ranged from 32.5 to 36.5 in each treatment group.

In Study 16, there were notable between-group differences in the categorization of patients according to the El Escorial diagnostic criteria, with 20.2% versus 28.7% categorized as "definite ALS" and 26.9% versus 19.8% categorized as "probable ALS – laboratory supported" in the placebo versus edaravone groups. Also, mean disease duration was 1.30 years in the placebo group and 1.44 years in the edaravone group. In Study 17, there were notable between-group differences in sex and diagnostic categorization among the patients who had received edaravone in Study 16. The proportion of male patients was 72.7% versus 54.2% and the proportion of patients categorized as "definite ALS" was 25.0%

versus 29.2% in the edaravone-placebo group versus the edaravone-edaravone group. In Study 18, there were notable differences between the placebo and edaravone groups in mean disease duration (2.05 years versus 1.75 years), patients whose initial ALS symptoms were bulbar (0% versus 23.1%), patients categorized as “definite ALS” (16.7% versus 53.8%) and “probable ALS” (66.7% versus 30.8%), and patients on concomitant riluzole (91.7% versus 75.0%). In Study 19, there were notable between-group differences in the Japanese ALS severity classification, with 76.5% in the placebo group and 68.1% in the edaravone group having grade 2 ALS.

Table 5: Summary of Baseline Characteristics

	Study 16 FAS		Study 17[a] FAS			Study 18 FAS		Study 19 FAS	
	PL N = 104	ED N = 101	ED-PL N = 44	ED-ED N = 48	PL-ED N = 88	PL N = 12	ED N = 13	PL N = 68	ED N = 69
Male, n (%)	69 (66.3)	63 (62.4)	32 (72.7)	26 (54.2)	57 (64.8)	6 (50.0)	7 (53.8)	41 (60.3)	38 (55.1)
Age in years, mean (SD)	57.7 (10.2)	57.9 (9.8)	55.5 (10.1)	59.6 (9.8)	56.9 (10.4)	59.8 (7.6)	57.5 (7.1)	60.1 (9.6)	60.5 (10.1)
Height in cm, mean (SD)	163.4 (8.2)	162.9 (8.3)	164.5 (7.4)	161.8 (9.0)	163.5 (7.7)	160.9 (10.5)	164.4 (8.4)	162.5 (8.4)	161.8 (9.5)
Weight in kg, mean (SD)	59.0 (12.1)	58.3 (8.8)	59.7 (8.7)	57.2 (8.9)	59.4 (10.4)	55.0 (8.2)	53.4 (10.9)	57.8 (9.3)	57.9 (12.9)
Disease duration in years, mean (SD)	1.30 (0.63)	1.44 (0.63)	1.45 (0.61)	1.48 (0.66)	1.31 (0.61)	2.05 (0.59)	1.75 (0.59)	1.06 (0.47)	1.13 (0.46)
Initial symptom classification, n (%)									
Bulbar	20 (19.2)	18 (17.8)	7 (15.9)	9 (18.8)	17 (19.3)	0 (0.0)	3 (23.1)	14 (20.6)	16 (23.2)
Limb	84 (80.8)	83 (82.2)	37 (84.1)	39 (81.3)	71 (80.7)	12 (100.0)	10 (76.9)	54 (79.4)	53 (76.8)
ALS diagnosis, n (%)									
Sporadic	100 (96.2)	100 (99.0)	44 (100.0)	47 (97.9)	84 (95.5)	11 (91.7)	13 (100.0)	66 (97.1)	68 (98.6)
Familial	4 (3.8)	1 (1.0)	0	1 (2.1)	4 (4.5)	1 (8.3)	0	2 (2.9)	1 (1.4)
El Escorial revised Airlie House diagnostic criteria, n (%)									
Definite ALS	21 (20.2)	29 (28.7)	11 (25.0)	14 (29.2)	18 (20.5)	2 (16.7)	7 (53.8)	27 (39.7)	28 (40.6)
Probable ALS	54 (51.9)	52 (51.5)	23 (52.3)	24 (50.0)	46 (52.3)	8 (66.7)	4 (30.8)	41 (60.3)	41 (59.4)
Probable ALS laboratory supported	28 (26.9)	20 (19.8)	10 (22.7)	10 (20.8)	23 (26.1)	2 (16.7)	2 (15.4)	NA	NA
Possible ALS	1 (1.0)	0	0	0	1 (1.1)	0	0	NA	NA
Japanese ALS severity classification, n (%)									
Grade 1	40 (38.5)	36 (35.6)	7 (15.9)	6 (12.5)	9 (10.2)	NA	NA	16 (23.5)	22 (31.9)
Grade 2	64 (61.5)	65 (64.4)	23 (52.3)	26 (54.2)	48 (54.5)	NA	NA	52 (76.5)	47 (68.1)
Grade 3	NA	NA	11 (25.0)	12 (25.0)	18 (20.5)	12 (100.0)	13 (100.0)	NA	NA

	Study 16 FAS		Study 17[a] FAS			Study 18 FAS		Study 19 FAS	
	PL N = 104	ED N = 101	ED-PL N = 44	ED-ED N = 48	PL-ED N = 88	PL N = 12	ED N = 13	PL N = 68	ED N = 69
Grade IV	NA	NA	3 (6.8)	2 (4.2)	11 (12.5)	NA	NA	NA	NA
Grade V	NA	NA	0	1 (2.1)	1 (1.1)	NA	NA	NA	NA
Missing	NA	NA	0	1 (2.1)	1 (1.1)	NA	NA	NA	NA
ALSFRS-R score, mean (SD)									
Before pre-registration	43.3 (2.6)	42.5 (3.4)	NA	NA	NA	36.8 (3.6)	34.5 (5.4)	43.5 (2.2)	43.6 (2.2)
At baseline	41.2 (2.9)	40.6 (3.5)	36.5 (5.5)	36.0 (6.1)	35.8 (7.0)	34.6 (3.3)	32.5 (5.5)	41.8 (2.2)	41.9 (2.4)
Change from pre-registration to baseline, n (%)									
−4	11 (10.6)	8 (7.9)	5 (11.4)	1 (2.1)	8 (9.1)	2 (16.7)	2 (15.4)	3 (4.4)	5 (7.2)
−3	21 (20.2)	21 (20.8)	6 (13.6)	12 (25.0)	18 (20.5)	2 (16.7)	2 (15.4)	8 (11.8)	7 (10.1)
−2	39 (37.5)	32 (31.7)	17 (38.6)	13 (27.1)	32 (36.4)	4 (33.3)	4 (30.8)	25 (36.8)	21 (30.4)
−1	33 (31.7)	40 (39.6)	16 (36.4)	22 (45.8)	30 (34.1)	4 (33.3)	5 (38.5)	32 (47.1)	36 (52.2)
Concomitant riluzole, n (%)	92 (88.5)	90 (89.1)	38 (86.4)	42 (87.5)	79 (89.8)	11 (91.7)	10 (76.9)	62 (91.2)	63 (91.3)
Concomitant drugs other than riluzole, n (%)	103 (99.0)	100 (99.0)	44 (100.0)	47 (97.9)	88 (100.0)	12 (100.0)	13 (100.0)	67 (98.5)	68 (98.6)

ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; ED = edaravone; FAS = full analysis set; NA = not applicable; PL = placebo; SD = standard deviation.

[a] ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17. PL-ED refers to the group receiving placebo in Study 16 and edaravone in Study 17. Baseline characteristics for Study 17 are from baseline in cycle 1 (start of Study 16), except for the Japanese ALS severity classification, ALSFRS-R score, and concomitant riluzole, which were reported from baseline in cycle 7 (start of Study 17).

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] MCI186-18,[13] and MCI186-19.[14]

Interventions

Patients were randomized for both their Study 16 and Study 17 treatments at the beginning of Study 16. Patients were assigned using dynamic allocation, specifically, the minimization method, in blocks of four. Factors used for dynamic allocation were change in ALSFRS-R score over the 12-week pre-observation period (−4 to −3 or −2 to −1), concomitant riluzole use (yes or no), and initial symptom classification (bulbar or limb). Zelen's method was used for institutional balancing. In Study 18, patients were randomized using the minimization method in blocks of four, and change in ALSFRS-R score over the 12-week pre-observation period (−4 to −3 or −2 to −1) was used as a dynamic allocation factor. Zelen's method was also used in this trial. In Study 19, patients were randomized using the minimization method in blocks of 20 and the dynamic allocation factors were change in ALSFRS-R score over the 12-week pre-observation period (−4 to −3 or −2 to −1), El Escorial diagnostic criteria (definite ALS or probable ALS), and age (at least 65 years or less than 65 years old).

The interventions were identical in all four RCTs. Two ampoules, each containing 60 mg of edaravone or placebo matched to edaravone in appearance, were diluted in saline before being intravenously infused over 60 minutes once a day. Patients could be administered

study treatment on an in-patient or outpatient basis. In the first treatment cycle in studies 16, 18, and 19, the study treatment was administered daily for 14 consecutive days, followed by a two-week period with no study treatment administration. In subsequent treatment cycles (including the first cycle in Study 17), the study treatment was administered for a total of 10 days within the first 14 days, followed by a two-week treatment-free period. In all four RCTs, double-blind study treatment lasted for six treatment cycles or a total of 24 weeks. In Study 17, the six treatment cycles were followed by three more treatment cycles in which all patients received edaravone. The results for the last three treatment cycles in Study 17 and for the placebo-edaravone group are not included in this report.

Treatment allocation was done through a central registration centre and study investigators or other personnel received the number corresponding to the assigned study medication. Study treatment ampoules were packaged in boxes and the labels on the ampoules and boxes were identical regardless of treatment. At two time points during the study, the study drug assignment manager confirmed the indistinguishability of the edaravone and placebo products in terms of appearance and packaging. Patients in Study 17 were aware of their treatment allocation in Study 16 and patients who received placebo in Study 16 would have known they were receiving edaravone in Study 17.

The concomitant use of riluzole with no change in dose or administration route during the trials was allowed, though riluzole therapy could not be initiated during the trials. Concomitant use of other drugs and therapies was allowed, except for meloxicam, levocarnitine, sodium valproate, and high doses or intramuscular doses of mecobalamin (vitamin B12), in studies 16, 17, and 18, and high doses or intramuscular doses of mecobalamin and tauroursodeoxycholic acid in Study 19. Concomitant drugs and therapies were recorded in each trial.

Outcomes

The primary efficacy end point in studies 16, 17, and 19 was change in ALSFRS-R total score from baseline to the end of treatment (end of cycle 6). The same end point was assessed in Study 18, although Study 18 was an exploratory study. All of the efficacy outcomes were administered by investigators or sub-investigators.

The ALSFRS-R is a questionnaire-based scale that was designed to allow clinicians to quickly measure the functionality or physical function regarding activities of daily living (ADLs) for patients living with ALS.[38-40] The ALSFRS-R is composed of 12 questions that cover four main domains: gross motor activity, fine motor activity, respiratory function, and nutrition. Each question is scored on a five-point scale from zero to four, where zero = absent function and four = no impairment. The score for each question is summed for an overall score ranging from zero to 48. The ALSFRS-R total score has demonstrated acceptable internal consistency reliability as well as construct validity when compared with the Sickness Impact Profile.[40] However, the correlation of the respiratory subscale score with FVC was found to be poor.[40] Acceptable test–retest reliability was demonstrated for each item in the original (unrevised) ALSFRS, which did not include the questions on dyspnea, orthopnea, and respiratory insufficiency.[39] No information was identified with respect to the test–retest reliability for the ALSFRS-R. In a group of 42 ALS clinical experts, 93% and 100% considered a decrease in the slope of the ALSFRS-R score over time of 20% and 25%, respectively, to be at least “somewhat clinically meaningful.”[38] The clinical experts consulted by CADTH commented that the slope of the score change of 20% to 25% is likely clinically meaningful. One study of 30 patients with ALS found that a one-unit

change in patient-perceived clinical function paralleled a nine-point decrease in the ALSFRS-R score (P = 0.025; 95% CI, 8 to 10).[41] Formally calculated minimal clinically important differences (MCIDs) for the total score or individual subscale scores were not found.

In the four RCTs, subscale scores were reported for the bulbar (three items with possible scores ranging from 0 to 12), limb (six items with possible scores ranging from 0 to 24), and respiratory (three items with possible scores ranging from 0 to 12) domains of the ALSFRS-R.

The following secondary efficacy outcomes were assessed in the four RCTs:

- the occurrence of death or certain disease progression
- Modified Norris Scale (composed of the Limb Norris Scale and Norris Bulbar Scale)
- grip and pinch-grip strength
- FVC percentage
- 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40)
- Japanese ALS severity classification.

The following events were summarized in the four RCTs for death or certain disease progression: death, disability of independent ambulation, loss of upper-limb function, tracheotomy, use of respirator, and use of tube feeding. The loss of useful speech was also summarized in Study 19. Disability of independent ambulation was defined as a score of two points or worse ("walks with assistance") on the "walking" item of the ALSFRS-R. Loss of upper-limb function was defined as a score of zero points for all of the following items of the ALSFRS-R: "handwriting," "eating motion," and "dressing and hygiene." The use of a respirator did not include BiPAP use. Patients who scored zero points ("exclusively parenteral or enteral feeding") for the ALSFRS-R item "swallowing" were considered to use tube feeding.

Besides the ALSFRS-R, motor function as well as grip and pinch-grip strength were also assessed with the Modified Norris Scale. The Modified Norris Scale is used to evaluate the functional ability of patients with ALS and is composed of two parts.[42] The first is referred to as the Limb Norris Scale, which includes 21 items regarding ADLs related to the extremities, such as "hold up head," "buttoning, zipping," and "stand up."[23] The second part, the Norris Bulbar Scale, is composed of 13 items that are used to evaluate bulbar function, or function relating to speech and swallowing.[23] Each item is scored on an ordinal four-point scale, corresponding to the following values and ratings or functional scores: normal (3 points) to somewhat impaired (2 points), inadequate (1 point), and "cannot do at all" (0 points). Both the Limb Norris Scale and Norris Bulbar Scale are totalled by summing the scores, for a minimum of zero or a maximum score of 63 points and 39 points, respectively. A higher score indicates better functional ability. The total scores for the limb and bulbar scales have demonstrated acceptable inter-rater reliability.[42] An MCID was not identified for the Modified Norris Scale.

Grip strength and pinch-grip strength were measured in both hands, with pinch-grip strength measured by opposing the pulp of the thumb and the side of the index finger. Grip strength was reported as the mean value of both hands.

Respiratory function was assessed using FVC, which is the volume of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. FVC can be

reported as a percentage of the volume predicted for a person of the same size, age, and sex. While an MCID was not found for patients with ALS, MCIDs for decline in function have been identified for patients with idiopathic pulmonary fibrosis (2% to 6%[43]) and scleroderma (3.0% to 3.3%[44]).

The ALS Assessment Questionnaire (ALSAQ-40) is a 40-item, disease-specific questionnaire that was created specifically to assess the health-related quality of life (HRQoL) of patients with ALS.[45-47] It is composed of five dimensions corresponding to: eating and drinking (3 items), communication (7 items), ADL/independence (10 items), mobility (10 items), and emotional well-being (10 items).[45] The questionnaire is completed by patients based on a two-week recall of experiences they may have had, which are rated by frequency of occurrence on a five-point Likert scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always or cannot do at all).[48] Each scale is then converted to a summary score from zero (best health status) to 100 (worst health status) by dividing the total raw score of each item by the maximum possible total raw score of all scale items, then multiplying that by 100.[45] The ALSAQ-40 has also been translated and validated in various languages other than English, including Japanese.[49] The ALSAQ-40 has acceptable internal consistency reliability for each dimension as well as construct validity for the eating and drinking, physical mobility, and emotional functioning dimensions.[46,47] MCIDs have been identified for the summary scores for each dimension: 3.35 for physical mobility, 5.67 for ADL/independence, 6.40 for eating and drinking, 6.67 for communication, and 2.67 for emotional functioning.[50] In the four RCTs, a total score for the ALSAQ-40 was reported as the sum of the scores for all the items (yielding a range of possible scores of 0 to 200), as opposed to individual summary scores for each dimension. An MCID for the total score was not found.

Overall disease severity was assessed using the Japanese ALS severity classification, which is based on a rating of the functional ability of patients. The level of functionality is classified into one of five categories on an ordinal scale, with 1 representing the least amount of functional impairment associated with severity of disease, and 5 representing the most. The scales are defined as follows: 1 = able to work or perform housework; 2 = independent living but unable to work; 3 = requiring assistance for eating, excretion, or ambulation; 4 = presence of respiratory insufficiency, difficulty in coughing out sputum or dysphagia; 5 = using a tracheostomy tube, tube feeding, or tracheostomy positive-pressure ventilation.[23] Information regarding the validity or reliability of this scale or an MCID was not identified.

The ALSFRS-R, FVC, and grip strength were assessed at the start of the treatment period (and the start of the pre-observation period for the ALSFRS-R and FVC) in studies 16, 18, and 19, and at the end of each treatment cycle or at discontinuation in all four RCTs. The Norris scales, ALSAQ-40, and Japanese ALS severity classification were assessed at the start of the treatment period (and the start of the pre-observation period in the case of the ALS severity classification) in studies 16, 18, and 19, and at the end of the sixth treatment cycle or at discontinuation in all four RCTs. Deaths and disease-progression events occurring during the period from the start of treatment to the end of the sixth treatment cycle or two weeks after discontinuation (the last day of the discontinued treatment cycle in Study 16) were assessed.

Outcomes related to hospitalizations and caregiver burden were not assessed in the RCTs.

The safety of edaravone was assessed by reporting AEs that occurred during the period from the start of treatment to the end of the sixth treatment cycle or two weeks after discontinuation.

Statistical Analysis

The primary efficacy end point in the four RCTs was change in the mean total ALSFRS-R score from baseline to the end of treatment (end of cycle 6). The superiority of edaravone over placebo was tested using a linear regression model that adjusted for the dynamic allocation factors and a two-sided significance level of 5%. No adjustment was made for multiplicity. In Study 16, a second method of analysis for the primary end point was conducted using a repeated-measures analysis of variance (ANOVA) model. The ANOVA model included treatment, time, interaction of treatment and time, baseline value, and the dynamic allocation factors. There was no control for type I error for the two methods of analysis. In subgroup analyses in studies 16, 17, and 19, the primary end point was compared between treatment groups using a two-sample *t*-test with patients stratified into subgroups by either duration of disease (less than one year, one year to less than two years, or at least two years), Japanese ALS severity classification (by baseline grade), or initial symptom category (bulbar or limb).

The same linear regression model used for the primary end point was used to evaluate change in the ALSFRS-R domain scores, Modified Norris Scale score (including the limb and bulbar scales individually), ALSAQ-40 score, grip strength (mean of both hands), and pinch-grip strength (mean of both hands). A shift table was used to summarize the Japanese ALS severity grade at baseline and at the end of treatment.

Measurements that were taken outside of the permitted time ranges for each assessment time point were handled as missing data. For the continuous efficacy outcomes, last observation carried forward (LOCF) was used for patients who completed the third treatment cycle.

Time to death or certain disease progression was analyzed using a Kaplan–Meier plot, a log-rank test, and a generalized Wilcoxon test. In studies 16, 17, and 18, the log-rank and Wilcoxon tests were stratified on the change in ALSFRS-R score during the pre-observation period (−4 to −3 or −2 to −1). In patients experiencing multiple events, the first event was considered the event onset day.

The sample-size calculations for Study 16 were based on the results of a previous phase II study that showed a change in ALSFRS-R score over six months of −4.6 in the placebo group and −2.4 in the edaravone group, with a pooled standard deviation (SD) of 4.3. Using a two-sample *t*-test, the planned 100 patients per group would yield 95% power at a significance level of 0.05. Study 18 was considered to be an exploratory study and no rationale was given for the planned sample size. The sample-size calculations for Study 19 were based on the results of a post hoc analysis of Study 16. In the post hoc–defined subgroup on which the study selection criteria for Study 19 were based, a between-group difference in change in ALFRS-R score of 3.0 with an SD of 6.0 was assumed. Using a two-sided significance level of 0.05, the planned sample size of 64 patients per group would yield 80% power.

Analysis Populations

The full analysis set was defined as all randomized patients who received the study treatment and had efficacy data available. Patients with a disease other than ALS were

excluded from the full analysis set in all the trials. Patients with significant Good Clinical Practice (GCP) violations were excluded from the full analysis set in studies 16, 17, and 18.

The per-protocol set was defined as all patients in the full analysis set except for those who did not meet study selection criteria, used a prohibited concomitant medication or initiated riluzole treatment, or received 70% or less of the treatments specified in the protocol.

The safety analysis set was defined as all randomized patients who received the study treatment, had efficacy (in studies 16 and 18) or safety data (studies 17 and 19) available, and did not have significant GCP violations (in studies 16, 17, and 18).

The numbers of patients in each analysis set are provided in Table 6.

Patient Disposition

Details on patient disposition are provided in Table 6. All patients who were randomized received at least one infusion of the study treatment. In Study 16, 13.5% versus 8.8% of patients discontinued the study in the placebo versus edaravone groups, with the most common reasons being patient decision and AE. The difference in discontinuations between groups was driven by AEs (5.8% versus 3.0% in the placebo versus edaravone group). In Study 17, 15.6% versus 29.2% discontinued the extension study in the placebo versus edaravone groups, with the most common reasons being tracheotomy and AE. A greater proportion of patients in the edaravone-edaravone group discontinued due to tracheotomy than in the edaravone-placebo group (14.6% versus 2.3%). In Study 18, 30.8% of patients in the edaravone discontinued, with the reasons being patient decision and AE. In Study 19, 11.8% in the placebo group and 2.9% in the edaravone group discontinued, with more patients in the placebo group discontinuing due to patient decision, AE, and investigator decision.

Table 6: Patient Disposition

	Study 16		Study 17			Study 18		Study 19	
	PL	ED	ED-PL	ED-ED	PL-ED	PL	ED	PL	ED
Screened (pre-registered), N	246		NA			27		192	
Randomized (registered)									
Per treatment group, N	104	102	45	48	88	12	13	68	69
Received assigned treatment									
Per treatment group, N (%)	104 (100)	102 (100)	45 (100)	48 (100)	88 (100)	12 (100)	13 (100)	68 (100)	69 (100)
Completed the study									
Per treatment group, N (%)	90 (86.5)	93 (91.2)	38 (84.4)	34 (70.8)	72 (81.8)	12 (100)	9 (69.2)	60 (88.2)	67 (97.1)
Discontinued, N (%)									
Per treatment group, N (%)	14 (13.5)	9 (8.8)	7 (15.6)	14 (29.2)	16 (18.2)	0	4 (30.8)	8 (11.8)	2 (2.9)
Reason for discontinuation, N (%)									
Patient decision	5 (4.8)	5 (5.0)	4 (9.1)	2 (4.2)	5 (5.7)	0	2 (15.4)	2 (2.9)	0
Difficult to continue due to AE	6 (5.8)	3 (3.0)	2 (4.5)	3 (6.3)	2 (2.3)	0	1 (7.7)	2 (2.9)	0
Tracheotomy due to worsening condition	2 (1.9)	1 (1.0)	1 (2.3)	7 (14.6)	6 (6.8)	0	0	1 (1.5)	1 (1.4)
Protocol deviation	1 (1.0)	0	0	0	0	0	0	0	0
Patient convenience	0	0	0	0	1 (1.1)	0	1 (7.7)	0	0

	Study 16		Study 17			Study 18		Study 19	
FVC ≤ 50% and $paCO_2$ (blood gas) of ≥ 45 mm Hg	0	0	0	0	0	0	0	1 (1.5)	1 (1.4)
Investigator decision, other	0	0	0	2 (4.2)	2 (2.3)	0	0	1 (1.5)	0
All-day respiratory support was needed	0	0	0	0	0	0	0	1 (1.5)	0
FAS, N	104	101	44	48	88	12	13	68 (100)	69 (100)
PP, N	98	97	42	46	84	12	12	63 (92.6)	68 (98.6)
Safety, N	104	102	45	48	88	12	13	68 (100)	69 (100)

AE = adverse event; ED = edaravone; FAS = full analysis set; FVC = functional vital capacity; NA = not applicable; $PaCO_2$ = partial pressure of carbon dioxide; PL = placebo; PP = per-protocol.

Note: ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17. PL-ED refers to the group receiving placebo in Study 16 and edaravone in Study 17.

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] MCI186-18,[13] and MCI186-19.[14]

Exposure to Study Treatments

Treatment adherence was defined as the number of treatment administrations as a percentage of planned treatment administrations. In studies 16, 18, and 19, 89% or more in each treatment group had 100% treatment adherence. In Study 17, the extension study, the proportion of patients in each group with 100% treatment adherence ranged from 77.1% to 88.6%. While there were some differences in treatment adherence in Study 17 between the edaravone-placebo and edaravone-edaravone groups (15.9% versus 22.9% with 90% to 100% adherence and 4.5% versus 0% with 80% to 90% adherence), no patients had less than 80% adherence. In Study 19, there were between-group differences in patients with less than 70% adherence (7.4% versus 1.4% for placebo versus edaravone) and between 90% and 100% adherence (1.5% versus 8.7% for placebo versus edaravone).

Table 7: Treatment Adherence

	Study 16 FAS		Study 17 FAS			Study 18 FAS		Study 19 FAS	
	PL N = 104	ED N = 101	ED-PL N = 44	ED-ED N = 48	PL-ED N = 88	PL N = 12	ED N = 13	PL N = 68	ED N = 69
Treatment adherence, N (%)									
100%	96 (92.3)	95 (94.1)	35 (79.5)	37 (77.1)	78 (88.6)	12 (100.0)	13 (100.0)	61 (89.7)	62 (89.9)
≥ 90%, < 100%	6 (5.8)	5 (5.0)	7 (15.9)	11 (22.9)	6 (6.8)	0	0	1 (1.5)	6 (8.7)
≥ 80%, < 90%	2 (1.9)	1 (1.0)	2 (4.5)	0 (0.0)	2 (2.3)	0	0	1 (1.5)	0
≥ 70%, < 80%	0	0	0	0	2 (2.3)	0	0	0	0
< 70%	0	0	0	0	0	0	0	5 (7.4)	1 (1.4)

ED = edaravone; FAS = full analysis set; PL = placebo.

Note: ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17. PL-ED refers to the group receiving placebo in Study 16 and edaravone in Study 17.

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] MCI186-18,[13] and MCI186-19.[14]

Critical Appraisal

Internal Validity

The risk of bias from randomization, allocation, and blinding was low in studies 16, 18, and 19, as appropriate measures (central registration centre, identical packaging, and indistinguishability of placebo from edaravone) were taken to randomize patients, and to conceal treatment allocation from and maintain blinding of study personnel, investigators, and patients. Randomization may not have been maintained from the baseline of Study 16 to the baseline of Study 17, as 12% of patients discontinued during that time period and the characteristics of those patients were not reported.

There were imbalances between treatment groups in each study with regard to study discontinuations, with greater than 10% of patients discontinuing in some treatment groups. In studies 16 and 19, greater proportions of patients in the placebo groups discontinued, while the opposite was true in studies 17 and 18. The between-group difference was greatest in Study 17, with 15.6% in the edaravone-placebo group and 29.2% in the edaravone-edaravone group discontinuing. Given that LOCF was used for missing data in patients who completed three treatment cycles and that ALS is associated with a steady decline in motor function, the direction of potential bias would have favoured the treatment group with the greater proportion of discontinuations (provided they occurred following the third treatment cycle). Under this rationale, only studies 17 and 18 were at risk of bias in favour of edaravone.

There were some notable imbalances in baseline characteristics. In Study 16, patients in the placebo group were more likely to be categorized as “probable ALS – laboratory support” and patients in the edaravone group were more likely to be categorized as “definite ALS.” Due to the small sample size in Study 18, there were notable imbalances in several characteristics, including disease duration, initial ALS symptom, diagnostic category, and riluzole use. In Study 19, patients in the placebo group were more likely than patients in the edaravone group to have grade 2 ALS. However, the baseline ALSFRS-R scores were balanced between treatment groups in each study and the experts consulted for this review did not consider any of the between-group differences to be of concern.

The efficacy outcomes measures varied in terms of the evidence found for validity, reliability, and responsiveness. The ALSFRS-R is a well-studied tool with demonstrated construct validity and internal consistency reliability. However, the respiratory subscale does not correlate strongly with FVC and the MCID for the slope of the ALSFRS-R score over time is based on expert opinion. Unlike in deaths and events of disease progression, there is a degree of subjectivity in the items of the ALSFRS-R. However, the FDA supports the use of the ALSFRS-R as a measure of efficacy for ALS treatment by the demonstration of a treatment effect on function in daily living.[51] The total scores for the limb and bulbar scales of the Modified Norris Scale are reliable, but information on validity and responsiveness was not found. The validity and reliability of the grip and pinch-grip strength measurements are unclear as details on the methods for measuring them were not provided. FVC is a commonly used measure of respiratory function, though an MCID specific to patients with ALS was not found. The ALSAQ-40 has demonstrated construct validity for the summary scores for three of the five dimensions and acceptable internal consistency reliability for each dimension, but test–retest reliability information was not found. While MCIDs were found for each summary score of the ALSAQ-40, the RCTs used a total score for which no MCID was found.

The clinical experts consulted for this review indicated that the treatment period of six months was adequate to assess functional measures in ALS. However, the period is insufficient for evaluating event-free survival for a cohort of subjects in a phase of the disease where lung function and ambulation are largely preserved. While Study 17 assessed patients up to their 48th week of treatment with edaravone, there was no corresponding group that was treated with placebo for 48 weeks.

The methods of statistical analysis in the trials were appropriate and adjusted for potential confounders. There was no adjustment for multiplicity and conclusions cannot be made for any outcomes aside from the primary end point. Conclusions also cannot be made regarding the subgroup analyses, as they were not controlled for multiplicity, did not incorporate interaction terms between treatment and stratification factors, and were not a part of the sample-size considerations.

Rationales were provided for the planned sample sizes in studies 16 and 19, though the sample size in Study 16 was based on the results of 10 patients with grade 1 or 2 ALS[11] from a previous phase II study.[52] In that study, change in ALSFRS-R score in the six months before the initiation of edaravone treatment served as each patient's control. While the Study 16 sample size was based on a conservative statistical power of 95%, uncertainty in the results from the 10 patients could have led to underestimation of statistical power. Study 18 was an exploratory study with no rationale provided for the planned sample size and conclusions cannot be drawn about statistical power for the primary end point. In studies 16 and 19, the numbers of patients randomized met the planned sample sizes. The numbers of patients who completed the studies were less than the planned sample sizes in Study 16 and close to the planned samples sizes in Study 19.

External Validity

Population

The RCTs were conducted in Japan. The clinical experts consulted for this review were not aware of any factors that would limit the generalizability of the results to the Canadian setting, aside from possible differences in standard of care. The manufacturer published a study[53] simulating the pharmacokinetics of edaravone using pharmacokinetic models based on data from male Japanese and male and female Caucasian healthy volunteers. The study concluded that no clinically relevant differences in pharmacokinetic profiles were demonstrated between the Japanese and Caucasian simulated cohorts. However, the clinical efficacy of edaravone has yet to be compared between Japanese patients with ALS and patients of other ethnicities with ALS. The manufacturer also published a review[26] of guidelines and clinical trial patient characteristics in Japan, the US, and Europe. The authors of the review concluded that the evidence suggested that guidelines for the management of ALS and the characteristics of study patients with ALS were similar between Japan, the US, and Europe, with the exception of the use of invasive ventilation. The study populations represented patients in the earlier stages of ALS who did not have respiratory impairment and who were not likely to require invasive ventilation during the studies.

The study eligibility criteria in Study 16 restricted the study population to patients with a status of definite ALS, probable ALS, or "probable ALS – laboratory supported" with grade 1 or 2 severity who scored at least three points on all ALSFRS-R respiration items and who were within three years of disease onset. Study 18 included only patients with grade 3 severity, while those who continued from Study 16 to Study 17 represented patients of all

grades of severity, though less than 10% of the patients in each treatment group had grade 4 or 5 severity. Overall, most of the patients studied were classified as having grade 1 or 2 ALS severity. Study 19 had more restrictive criteria than Study 16, representing a subset of patients earlier in their disease course but with definite ALS or probable ALS. The clinical experts consulted for this review stated that the study populations were representative of a relatively early stage of the disease where lung function and ambulation are preserved, and that every ALS patient experiences a window during which they would be eligible for these studies. The chief difficulty in clinical practice would be to diagnose ALS while patients are still within that window. The clinical experts considered the observed baseline characteristics to be representative of those patients observed in the Canadian ALS population with preserved respiratory function and with functional independence.

Studies 16, 18, and 19 excluded patients who did not meet the criterion of having a one- to four-point decrease in ALSFRS-R score from the beginning to the end of the 12-week pre-observation period. This criterion made the rate of decline in motor function more homogeneous among the study patients and excluded those at the extremes of rate of decline. It also increased the probability of observing a mean decrease in ALSFRS-R score during the six-month treatment period.

Intervention

The edaravone regimen in the trials was the same as the Health Canada–approved recommended dosage and could be administered in either an in-patient or outpatient setting, thus reflecting the Canadian setting. According to the clinical experts, the treatment duration of six months was not long enough to study differences in mortality or other events related to disease progression. The European Medicines Agency guidance on studies of ALS treatments[54] supports this, stating that a “study duration of 12 to 18 months may be sufficient,” depending on assumptions of progression rates. Study 17 reported placebo-controlled efficacy data extending up to 48 weeks, and relevant safety data were reported for some patients on edaravone for up to 48 weeks in the Study 19 extension and up to 60 weeks in Study 17.

The prevalence of riluzole use and other concomitant treatments at baseline was similar to riluzole use and standard of therapy in Canada, according to the clinical experts consulted for this review.

Outcomes

The ALSFRS-R is a validated measure of motor function in patients with ALS and is commonly used in clinical trials in patients with ALS. While six months was not considered by the clinical experts consulted by CDR to be long enough to study overall survival, the outcomes identified in the systematic review protocol for motor function, HRQoL, and respiratory function were evaluated in the trials using valid outcome measures. However, caregiver burden and hospitalization, also identified in the systematic review protocol, were not assessed in the trials. The notable harms identified in the systematic review protocol would have been captured in the AE reporting in all the trials.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported subsequently (Table 3). Detailed efficacy outcomes are presented in Table 8.

Overall Survival

Survival Analysis for Death or Certain Disease Progression

In Study 16, 37 occurrences of death or certain disease-progression events were reported in the placebo group (35.6%) versus 38 occurrences (37.6%) in the edaravone group. In Study 17, the randomized extension of Study 16, a further 13 (29.5%) occurrences were reported in the edaravone-placebo arm as opposed to 19 (39.6%) in the edaravone-edaravone arm. In Study 18, a proportionally higher number of deaths and certain disease-progression events were reported in the edaravone arm (7 [53.8%]) versus the placebo arm (4 [33.3%]). Overall, deaths and certain disease-progression events were small in Study 19 compared with Study 16, with a higher number in the placebo arm (6 [8.8%]) than in the edaravone arm (2 [2.9%]). A breakdown based on the type of disease-progression event is available in Table 8. Survival analysis, using either the log-rank test or the generalized Wilcoxon test, did not show any differences between treatment groups in death or certain disease progression in any of the RCTs.

Assessment of Motor Function

ALSFRS-R Score (Primary End Point)

Studies 16, 17, 18, and 19 all reported on the change in ALSFRS-R at the end of six treatment cycles (with LOCF as an imputation method for missing data beyond the third treatment cycle). Study 16 showed no statistically significant differences in ALSFRS-R score between the edaravone and placebo groups, with a reported change from baseline of −5.70 (standard error [SE] = 0.85) in the edaravone group compared with −6.35 (SE = 0.84) in the placebo group (least squares mean [LSM] difference = 0.65 [95% CI, −0.90 to 2.19]). Similarly, Study 17 showed no statistically significant difference in ALSFRS-R score between the edaravone-edaravone and edaravone-placebo groups, with a reported change from baseline of −4.42 (SE = 0.69) in the edaravone-edaravone group compared with −5.58 (SE = 0.74) in the edaravone-placebo group (LSM difference = 1.16 [95% CI, −0.70 to 3.01]). Study 18 also showed no statistically significant differences in its exploratory outcomes of ALSFRS-R score between the edaravone and placebo groups, with a reported change from baseline of −6.52 (SE = 1.78) in the edaravone group compared with −6.00 (SE = 1.83) in the placebo group (LSM difference = −0.52 [95% CI, −5.62 to 4.58]). However, Study 19 did show a statistically significant difference in the change from baseline between the edaravone (−5.01 [SE = 0.064]) and placebo groups (−7.5 [SE = 0.66]), with an LSM difference of 2.49 (95% CI, 0.99 to 3.98) in favour of edaravone. Secondary and sensitivity analyses conducted in all studies for repeated measures and additional covariates showed results similar to the base case.

A change of nine points in the ALSFRS-R score was determined to be meaningful in one patient-centred study. The difference between edaravone and placebo did not reach this magnitude. However, a Delphi consensus study of clinical experts identified that a change of 20% or more in the slope of the ALSFRS-R decline was clinically meaningful; this magnitude of change was observed in Study 19, which was also a statistically significant result.

Subgroup analyses of the primary outcome are detailed in Table 9. All but one subgroup showed similar results to the base case. The one exception is the lack of a statistically significant difference in the subgroup of patients in Study 19 with bulbar initial symptoms.

A breakdown of the primary outcome within the three main domains (bulbar, limb, and respiratory) shows numerical differences in respiratory scores, bulbar scores, and limb scores between treatment groups. This is also reflected in the lack of statistical significance in the respiratory function score of Study 19. A detail of the breakdown of the primary outcome by each domain is presented in Table 10.

Total Modified Norris Scale Score (Secondary Outcome)

Studies 16, 17, 18, and 19 all reported on the change in the Modified Norris Scale score at the end of six treatment cycles (with LOCF as an imputation method for missing data beyond the third treatment cycle) as a secondary or exploratory outcome. There was no adjustment in the *P* value for multiple testing; thus, a statistically significant result should be interpreted with this in mind. Study 16 showed no statistically significant differences in Modified Norris Scale scores between the edaravone and placebo groups, with a reported change from baseline of −14.12 (SE = 2.05) in the edaravone group compared with −16.15 (SE = 2.00) in the placebo group (LSM difference = 2.03 [95% CI, −1.69 to 5.75]). Similarly, Study 17 showed no statistically significant difference for the change in the Modified Norris Scale score between the edaravone-edaravone and edaravone-placebo groups, with a reported change from baseline of −10.84 (SE = 1.68) in the edaravone-edaravone group compared with −14.02 (SE = 1.76) in the edaravone-placebo group (LSM difference = 3.19 [95% CI, −1.32 to 7.69]). Similarly, Study 18 showed no statistically significant differences in its exploratory outcome of Modified Norris Scale score between the edaravone and placebo groups, with a reported change from baseline of −18.18 (SE = 3.80) in the edaravone group compared with −17.76 (SE = 3.80) in the placebo group (LSM difference = −0.42 [95% CI, −11.27 to 10.44]). However, Study 19 did show a statistically significant difference in the change from baseline between the edaravone (−15.9 [SE = 1.97]) and placebo groups (−20.8 [SE = 2.06]), with an LSM of 4.89 (95% CI, 0.24 to 9.54) in favour of edaravone.

An MCID was not found for the Modified Norris Scale; thus, it is difficult to interpret the extent of the clinical importance of the reported statistically significant results from Study 19.

A breakdown of the Modified Norris Scale into the two main domains (bulbar and limb) no longer shows the statistically significant difference reported in Study 19. A detail of the breakdown of the Modified Norris Scale by each domain is presented in Table 11.

Grip Strength (Secondary Outcome)

Studies 16, 17, 18, and 19 all reported on the change in grip strength from baseline at the end of six treatment cycles (with LOCF as an imputation method for missing data beyond the third treatment cycle) as a secondary or exploratory outcome, with no adjustment in the *P* value for multiple testing; thus, any statistically significant result is nominal in nature. Study 16 showed no statistically significant differences in grip strength between the edaravone and placebo groups, with a reported change from baseline of −4.81 (SE = 0.69) in the edaravone group compared with −5.71 (SE = 0.69) in the placebo group (LSM difference = 0.89 [95% CI, −0.37 to 2.16]). Similarly, Study 17 showed no statistically significant difference in the change in grip strength between the edaravone-edaravone and edaravone-placebo groups, with a reported change from baseline of −3.10 (SE = 0.43) in the edaravone-edaravone group compared with −3.47 (SE = 0.45) in the edaravone-

placebo group (LSM difference = 0.38 [95% CI, −0.77 to 1.52]). Similarly, Study 18 showed no statistically significant differences in its exploratory outcome of grip strength between the edaravone and placebo groups, with a reported change from baseline of −3.06 (SE = 1.28) in the edaravone group compared with −3.72 (SE = 1.31) in the placebo group (LSM difference = 0.66 [95% CI, −3.00 to 4.33]). Similarly, Study 19 did not show a statistically significant difference in grip strength between the edaravone (−4.1 [SE = 0.54]) and placebo groups (−4.2 [SE = 0.56]), with an LSM of 0.11 (95% CI, −1.15 to 1.38).

Assessment of Respiratory Function

Forced Vital Capacity

Studies 16, 17, 18, and 19 all reported on the change in FVC from baseline at the end of six treatment cycles (with LOCF as an imputation method for missing data beyond the third treatment cycle) as a secondary or exploratory outcome, with no adjustment in the *P* value for multiple testing. Study 16 showed no statistically significant differences in FVC between the edaravone and placebo groups, with a reported change from baseline of −14.57 (SE = 2.41) in the edaravone group compared with −17.49 (SE = 2.39) in the placebo group (LSM difference = 2.92 [95% CI, −1.49 to 7.33]). Similarly, Study 17 showed no statistically significant difference in the change in FVC between the edaravone-edaravone and edaravone-placebo groups, with a reported change from baseline of −13.33 (SE = 2.29) in the edaravone-edaravone group compared with −10.15 (SE = 2.44) in the edaravone-placebo group (LSM difference = −3.17 [95% CI, −9.32 to 2.97]). Similarly, Study 18 showed no statistically significant differences between the edaravone and placebo groups in its exploratory outcome of FVC, with a reported change from baseline of −18.75 (SE = 4.58) in the edaravone group compared with −15.69 (SE = 4.58) in the placebo group (LSM difference = −3.06 [95% CI, −16.12 to 10.00]). Also showing similar statistically non-significant results, Study 19 did not show a statistically significant difference in the main analysis of FVC results between the edaravone (−15.6 [SE = 2.41]) and placebo groups (−20.4 [SE = 2.48]), with an LSM difference of 4.78 (95% CI, −0.83 to 10.40).

Assessment of Patients' Health-Related Quality of Life

ALSAQ-40 (Total Score)

Studies 16, 17, 18, and 19 all reported on the change in the ALSAQ-40 score at the end of six treatment cycles (with LOCF as an imputation method for missing data beyond the third treatment cycle) as a secondary or exploratory outcome, with no adjustment in the *P* value for multiple testing. Study 16 showed no statistically significant differences in ALSAQ-40 between the edaravone and placebo groups, with a reported change from baseline of 19.60 (SE = 3.82) in the edaravone group compared with 19.13 (SE = 3.79) in the placebo group (LSM difference = 0.48 [95% CI, −6.44 to 7.39]). Similarly, Study 17 showed no statistically significant difference in the change in the ALSAQ-40 score between the edaravone-edaravone and edaravone-placebo groups, with a reported change from baseline of 13.54 (SE = 2.89) in the edaravone-edaravone group compared with 18.99 (SE = 3.03) in the edaravone-placebo group (LSM difference = −5.45 [95% CI, −13.19 to 2.29]). Similarly, Study 18 showed no statistically significant differences in its exploratory outcome of ALSAQ-40 score between the edaravone and placebo groups, with a reported change from baseline of 20.91 (SE = 5.71) in the edaravone group compared with 26.33 (SE = 5.34) in the placebo group (LSM difference = −5.42 [95% CI, −21.05 to 10.20]). Conversely, Study 19 did show a statistically significant difference in the change from baseline between the edaravone (17.2 [SE = 3.39]) and placebo groups (26.0 [SE = 3.53]), with an LSM

difference of −8.79 (95% CI, −16.76 to −0.82), which favours the edaravone group over placebo.

An MCID was not found for total ALSAQ-40 score. However, the MCIDs for the ALSAQ-40 domains range from 2.67 points to 6.67 points. Thus, it is difficult to interpret the extent of the clinical importance of the reported total-score results.

Table 8: Key Efficacy Outcomes

	Study 16 FAS		Study 17 FAS		Study 18		Study 19 FAS	
Survival analysis for death or certain disease progression[a]	**PL N = 104**	**ED N = 101**	**ED-PL N = 44**	**ED-ED N = 48**	**PL N = 12**	**ED N = 13**	**PL N = 68**	**ED N = 69**
Total, N (%)	37 (35.6)	38 (37.6)	13 (29.5)	19 (39.6)	4 (33.3)	7 (53.8)	6 (8.8)	2 (2.9)
Deaths	2 (1.9)	2 (2.0)	1 (2.3)	1 (2.1)	0	1 (7.7)	0	0
Disability of independent ambulation	23 (22.1)	28 (27.7)	8 (18.2)	11 (22.9)	2 (16.7)	4 (30.8)	2 (2.9)	0
Loss of upper-limbs function	4 (3.8)	2 (2.0)	3 (6.8)	5 (10.4)	2 (16.7)	1 (7.7)	0	0
Tracheotomy	2 (1.9)	0	0	0	0	0	0	1 (1.4)
Use of respirator	3 (2.9)	1 (1.0)	0	1 (2.1)	0	0	0	0
Use of tube feeding	3 (2.9)	5 (5.0)	1 (2.3)	1 (2.1)	0	1 (7.7)	1 (1.5)	0
Loss of useful speech	NR	NR	NR	NR	NR	NR	3 (4.4)	1 (1.4)
P value for log-rank test[b]	0.3814		0.1540		0.1058		0.1284	
P value for generalized Wilcoxon test[b]	0.3992		0.0684		0.0782		0.1415	
Assessment of motor function using ALSFRS-R score (primary outcome)	**PL N = 99**	**ED N = 100**	**ED-PL N = 41**	**ED-ED N = 45**	**PL N = 12**	**ED N = 13**	**PL N = 66**	**ED N = 68**
Baseline, mean (SD)	41.2 (2.9)	40.6 (3.5)	36.5 (5.5)	36.0 (6.1)	34.6 (3.3)	32.5 (5.5)	41.8 (2.2)	41.9 (2.4)
End point, mean (SD)	35.1 (7.4)	35.3 (7.1)	31.5 (7.7)	32.3 (8.1)	29.2 (4.9)	26.6 (9.9)	35.0 (5.6)	37.5 (5.3)
Change from baseline, LS mean (SE)	−6.35 (0.84)	−5.70 (0.85)	−5.58 (0.74)	−4.42 (0.69)	−6.00 (1.83)	−6.52 (1.78)	−7.5 (0.66)	−5.01 (0.64)
Between-group difference, LS mean (95% CI)	0.65 (−0.90 to 2.19)		1.16 (−0.70, 3.01)		−0.52 (−5.62 to 4.58)		**2.49 (0.99 to 3.98)**	
P value	0.4108		0.2176		0.8347		**0.0013**	
Slope of change with time form baseline to end point, points per cycle (equal to month), LS mean (SE)	−1.05 (0.16)	−0.99 (0.16)	−1.62 (0.29)	−0.97 (0.28)	−0.96 (0.30)	−1.14 (0.29)	−1.35 (0.12)	−0.88 (0.12)
Between-group difference, LS mean (95% CI)	0.06 (−0.24 to 0.37)		0.66 (−0.09 to 1.41)		−0.18 (−1.02 to 0.66)		**0.47 (0.19 to 0.74)**	
P value	0.6785		0.0858		0.6614		**0.001**	
Assessment of motor function using Modified Norris Scale score (total score)	**PL N = 97**	**ED N = 95**	**ED-PL N = 41**	**ED-ED N = 45**	**PL N = 12**	**ED N = 12**	**PL N = 63**	**ED N = 68**
Baseline, mean (SD)	86.9 (9.6)	84.6 (11.1)	74.8 (17.2)	73.3 (16.3)	69.5 (13.2)	63.8 (18.6)	88.0 (6.7)	87.9 (7.8)
End point, mean (SD)	71.7 (19.3)	72.3 (18.9)	62.6 (21.8)	63.7 (20.1)	53.1 (15.0)	49.3 (25.9)	70.5 (16.7)	75.2 (15.4)

	Study 16 FAS		Study 17 FAS		Study 18		Study 19 FAS	
Change from baseline, LS mean (SE)	−16.15 (2.00)	−14.12 (2.05)	−14.02 (1.76)	−10.84 (1.68)	−17.76 (3.80)	−18.18 (3.80)	−20.8 (2.06)	−15.9 (1.97)
Between-group difference, LS mean (95% CI)	2.03 (−1.69 to 5.75)		3.19 (−1.32 to 7.69)		−0.42 (−11.27 to 10.44)		**4.89 (0.24 to 9.54)**	
P value	0.2835		0.1634		0.9371		**0.0393**	
Assessment of motor function using Grip Strength in kg	**PL N = 99**	**ED N = 100**	**ED-PL N = 41**	**ED-ED N = 45**	**PL N = 12**	**ED N = 13**	**PL N = 66**	**ED N = 68**
Baseline, mean (SD)	16.76 (11.08)	15.96 (10.01)	13.20 (10.05)	12.64 (10.45)	8.93 (9.04)	10.06 (8.32)	14.46 (8.81)	14.81 (8.94)
End point, mean (SD)	12.18 (10.20)	12.38 (10.02)	10.59 (10.28)	9.80 (9.35)	5.02 (6.58)	6.78 (7.58)	10.42 (8.58)	10.8 (8.59)
Change from baseline, LS mean (SE)	−5.71 (0.69)	−4.81 (0.69)	−3.47 (0.45)	−3.10 (0.43)	−3.72 (1.31)	−3.06 (1.28)	−4.19 (0.56)	−4.08 (0.54)
Between-group difference, LS mean (95% CI)	0.89 (−0.37, 2.16)		0.38 (−0.77 to 1.52)		0.66 (−3.00 to 4.33)		0.11 (−1.15 to 1.38)	
P value	0.1650		0.5173		0.7117		0.8583	
Assessment of respiratory function using FVC	**PL N = 99**	**ED N = 100**	**ED-PL N = 41**	**ED-ED N = 45**	**PL N = 12**	**ED N = 13**	**PL N = 66**	**ED N = 68**
Baseline, mean (SD)	95.78 (17.04)	95.53 (14.97)	88.18 (20.75)	84.52 (24.57)	86.48 (16.5)	83.9 (23.5)	97.37 (13.59)	100.50 (14.97)
End point, mean (SD)	80.12 (23.16)	83.11 (25.26)	80.08 (25.73)	75.46 (26.16)	71.47 (23.0)	62.6 (36.2)	80.48 (23.95)	87.64 (23.94)
Change from baseline, LS mean (SE)	−17.49 (2.39)	−14.57 (2.41)	−10.15 (2.44)	−13.33 (2.29)	−15.69 (4.58)	−18.75 (4.58)	−20.40 (2.48)	−15.61 (2.41)
Between-group difference, LS mean (95% CI)	2.92 (−1.49 to 7.33)		−3.17 (−9.32 to 2.97)		−3.06 (−16.12 to 10.00)		4.78 (−0.83 to 10.40)	
P value	0.1928		0.3074		0.6313		0.0942	
Assessment of patients' health-related quality of life using ALSAQ-40	**PL N = 95**	**ED N = 95**	**ED-PL N = 41**	**ED-ED N = 44**	**PL N = 12**	**ED N = 11**	**PL N = 64**	**ED N = 68**
Baseline, mean (SD)	92.5 (22.6)	97.6 (23.4)	110.2 (28.4)	118.3 (33.2)	112.1 (22.3)	122.2 (33.7)	91.4 (19.3)	89.1 (21.2)
End point, mean (SD)	110.9 (31.8)	116.2 (33.1)	125.6 (31.9)	128.7 (31.4)	137.1 (28.4)	139.6 (27.0)	117.2 (26.7)	105.7 (26.2)
Change from baseline, LS mean (SE)	19.13 (3.79)	19.60 (3.82)	18.99 (3.03)	13.54 (2.89)	26.33 (5.34)	20.91 (5.71)	26.04 (3.53)	17.25 (3.39)
Between-group difference, LS mean (95% CI)	0.48 (−6.44 to 7.39)		−5.45 (−13.19 to 2.29)		−5.42 (−21.05 to 10.20)		−8.79 (−16.76 to −0.82)	
P value	0.8921		0.1651		0.4773		**0.0309**	
Assessment of overall disease progression using the Japanese ALS severity classification	**PL N = 104**	**ED N = 101**	**ED-PL N = 44**	**ED-ED N = 48**	**PL N = 12**	**ED N = 13**	**PL N = 68**	**ED N = 69**
At baseline, N (%)								
Grade 1	40 (38.5)	36 (35.6)	7 (15.9)	6 (12.5)	NA	NA	16 (23.5)	22 (31.2)
Grade 2	64 (61.5)	65 (64.4)	23 (52.3)	26 (54.2)	NA	NA	52 (76.5)	47 (68.1)
Grade 3	NA	NA	11 (25)	12 (25)	12	13 (100)	NA	NA

	Study 16 FAS		Study 17 FAS		Study 18		Study 19 FAS	
					(100)			
Grade 4	NA	NA	3 (6.8)	2 (4.2)	NA	NA	NA	NA
Grade 5	NA	NA	0 (0)	1 (2.1)	NA	NA	NA	NA
Missing data	0	0	0 (0)	1 (2.1)	0	0	0	0
At end point, N (%)								
Grade 1	9 (8.7)	13 (12.9)	4 (9.1)	2 (4.2)	0	0	5 (7.4)	8 (11.6)
Grade 2	54 (51.9)	51 (50.5)	12 (27.3)	17 (35.4)	0	0	23 (33.8)	28 (40.6)
Grade 3	22 (21.2)	24 (23.8)	18 (40.9)	14 (29.2)	9 (75.0)	6 (46.2)	27 (39.7)	21 (30.4)
Grade 4	12 (11.5)	8 (7.9)	6 (13.6)	11 (22.9)	3 (25.0)	5 (38.4)	8 (11.8)	11 (15.9)
Grade 5	5 (4.8)	2 (2.0)	2 (4.5)	2 (4.2)	0	1 (7.7)	1 (1.5)	0
Missing data	2 (1.9)	3 (3.0)	2 (4.5)	2 (4.2)	0	1 (7.7)	4 (5.9)	1 (1.4)

ALS = amyotrophic lateral sclerosis; ALSAQ-40 = 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; CI = confidence interval; ED = edaravone; FAS = full analysis set; FVC = forced vital capacity; LOCF = last observation carried forward; LS = least squares; NA = not applicable; NR = not reported; PL = placebo; SD = standard deviation; SE = standard error.

Note: ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17.

Note: Efficacy data are reported for the period from the start of cycle 1 to the end of cycle 6 for studies 16, 18, and 19, and the period from the start of cycle 7 to the end of cycle 12 for Study 17.

Note: Continuous outcomes for all studies used LOCF for patients who completed the third treatment cycle and a linear regression model that adjusted for the dynamic allocation factors. The dynamic allocation factors for studies 16 and 17 were: ALSFRS-R score change during the pre-observation period, initial symptom, and concomitant use of riluzole. The dynamic allocation factor for Study 18 was ALSFRS-R score change during the pre-observation period. The dynamic allocation factors for Study 19 were: ALSFRS-R score change during the pre-observation period, EI Escorial revised Airlie House diagnostic category, and age (at least or less than 65 years).

[a] Death, disability of independent ambulation, loss of upper-limbs function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech.

[b] Stratified by change in ALSFRS-R score during the pre-observation period in studies 16, 17, and 18.

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] MCI186-18,[13] and MCI186-19.[14]

Table 9: Subgroup Analyses for the Primary End Point

	Study 16 FAS		Study 17 FAS		Study 19 FAS	
Assessment of motor function using ALSFRS-R Score (primary outcome)	**PL N = 104**	**ED N = 101**	**ED-PL N = 41**	**ED-ED N = 44**	**PL N = 68**	**ED N = 69**
Duration of disease						
< 1 year	**N = 35**	**N = 28**	**N = 12**	**N = 11**	**N = 32**	**N = 27**
Baseline, mean (SD)	37 (41.4)	29 (42.0)	37.9 (5.9)	38.2 (6.1)	42.1 (2.1)	42.8 (2.4)
End point, mean (SD)	35 (32.5)	28 (35.6)	32.5 (9.5)	34.5 (8.6)	35.0 (6.1)	38.2 (4.9)
Change from baseline, mean (SD)	−8.8 (7.4)	−6.3 (7.2)	−6.3 (6.3)	−4.1 (2.8)	−7.2 (5.3)	−4.6 (3.4)
P value for between-group difference	0.1916		0.3073		**0.0317**	
≥ 1 year and < 2 years	**N = 51**	**N = 49**	**N = 20**	**N = 24**	**N = 34**	**N = 41**
Baseline, mean (SD)	41.3 (2.9)	40.4 (2.8)	34.5 (5.0)	36.0 (5.2)	41.5 (2.4)	41.3 (2.3)
End point, mean (SD)	36.6 (5.6)	34.9 (5.6)	28.7 (6.4)	31.7 (8.2)	35.1 (5.2)	37.0 (5.5)
Change from baseline, mean (SD)	−4.7 (4.2)	−5.5 (4.2)	−5.9 (4.0)	−4.6 (4.5)	−6.5 (4.6)	−4.3 (4.1)
P value for between-group difference	0.3284		0.3493		**0.0288**	
≥ 2 years	**N = 13**	**N = 23**	**N = 9**	**N = 10**		
Baseline, mean (SD)	40.2 (3.4)	39.1 (4.6)	38.6 (4.9)	33.5 (7.4)	NA	NA
End point, mean (SD)	36.2 (6.0)	35.6 (7.4)	36.2 (5.6)	31.5 (7.6)	NA	NA
Change from baseline, mean (SD)	−4.0 (5.7)	−3.5 (4.8)	−3.0 (2.7)	−3.5 (3.7)	NA	NA
P value for between-group difference	0.7892		0.7411		NA	

	Study 16 FAS		Study 17 FAS		Study 19 FAS	
Japanese ALS severity classification						
Grade 1	**N = 38**	**N = 35**	**N = 7**	**N = 6**	**N = 16**	**N = 22**
Baseline, mean (SD)	43.0 (2.1)	43.0 (2.3)	43.1 (3.3)	42.5 (2.3)	43.3 (2.7)	43.5 (1.7)
End point, mean (SD)	39.4 (4.6)	39.2 (5.7)	39.0 (9.3)	40.5 (3.1)	38.1 (5.1)	41.0 (2.9)
Change from baseline, mean (SD)	−3.6 (4.0)	−3.8 (4.0)	−4.1 (7.1)	−2.0 (2.5)	−5.2 (4.5)	−2.5 (1.8)
P value for between-group difference	0.8349		0.4996		**0.0156**	
Grade 2	**N = 61**	**N = 65**	**N = 21**	**N = 25**	**N = 50**	**N = 46**
Baseline, mean (SD)	40.1 (2.8)	39.2 (3.3)	37.8 (3.3)	38.1 (4.0)	41.3 (1.9)	41.1 (2.4)
End point, mean (SD)	32.4 (7.6)	33.1 (6.9)	32.9 (5.6)	34.3 (6.4)	34.0 (5.4)	35.7 (5.3)
Change from baseline, mean (SD)	−7.5 (6.6)	−6.1 (5.9)	−5.4 (4.7)	−4.0 (3.9)	−7.4 (4.9)	−5.3 (4.2)
P value for between-group difference	0.1843		0.2710		**0.0310**	
Grade 3			**N = 10**	**N = 12**		
Baseline, mean (SD)	NA	NA	31.8 (3.7)	31.1 (3.9)	NA	NA
End point, mean (SD)	NA	NA	26.6 (4.7)	25.9 (6.2)	NA	NA
Change from baseline, mean (SD)	NA	NA	−5.6 (3.1)	−5.2 (3.6)	NA	NA
P value for between-group difference	NA		0.7675		NA	
Grade 4			**N = 3**	**N = 1**		
Baseline, mean (SD)	NA	NA	27.3 (1.2)	21.5 (3.5)	NA	NA
End point, mean (SD)	NA	NA	20.3 (2.1)	11.0 (NA)	NA	NA
Change from baseline, mean (SD)	NA	NA	−7.0 (1.0)	−13.0 (NA)	NA	NA
P value for between-group difference	NA		0.0351		NA	
Initial symptom category						
Bulbar	**N = 19**	**N = 17**	**N = 6**	**N = 7**	**N = 14**	**N = 15**
Baseline, mean (SD)	41.4 (2.6)	41.0 (2.5)	32.9 (5.3)	38.3 (4.7)	42.6 (1.9)	41.6 (2.2)
End point, mean (SD)	35.2 (8.4)	36.2 (5.5)	24.3 (6.8)	37.0 (6.7)	35.6 (4.1)	37.0 (5.4)
Change from baseline, mean (SD)	−6.2 (6.4)	−4.8 (4.2)	−8.3 (5.7)	−3.1 (3.9)	−6.9 (3.8)	−4.5 (3.9)
P value for between-group difference	0.4351		0.0794		0.1058	
Limb	**N = 80**	**N = 83**	**N = 35**	**N = 38**	**N = 52**	**N = 53**
Baseline, mean (SD)	41.2 (3.0)	40.5 (3.6)	37.1 (5.3)	35.4 (6.3)	41.6 (2.3)	42.0 (2.5)
End point, mean (SD)	35.1 (7.2)	35.1 (7.4)	32.7 (7.3)	31.5 (8.1)	34.9 (6.0)	37.6 (5.3)
Change from baseline, mean (SD)	−6.0 (5.9)	−5.4 (5.6)	−4.8 (4.3)	−4.4 (3.9)	−6.8 (5.2)	−4.4 (3.8)
P value for between-group difference	0.4981		0.6849		**0.0069**	

ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; ED = edaravone; FAS = full analysis set; LOCF = last observation carried forward; NA = not applicable; PL = placebo; SD = standard deviation.

Note: ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17.

Note: Efficacy data are reported for the period from the start of cycle 1 to the end of cycle 6 for studies 16, 18, and 19, and the period from the start of cycle 7 to the end of cycle 12 for Study 17.

Note: In studies 16 and 19, LOCF was used for patients who completed cycle 3. In Study 17, LOCF was used for patients who completed cycle 9.

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] and MCI186-19.[14]

Table 10: ALSFRS-R: Domain Scores for Bulbar, Limb, and Respiratory Function

	Study 16 FAS		Study 17 FAS		Study 18 FAS		Study 19 FAS	
Assessment of motor function using ALSFRS-R bulbar function score	**PL N = 99**	**ED N = 100**	**ED-PL N = 41**	**ED-ED N = 45**	**PL N = 12**	**ED N = 13**	**PL N = 66**	**ED N = 68**
Baseline, mean (SD)	10.7 (1.9)	10.4 (2.1)	9.8 (3.0)	9.2 (3.5)	11.6 (0.8)	10.0 (2.7)	10.8 (1.5)	10.6 (1.8)
End point, mean (SD)	9.6 (2.9)	9.3 (3.3)	9.0 (3.5)	8.8 (3.7)	10.3 (1.4)	8.2 (4.1)	9.2 (2.7)	9.7 (3.0)
Change from baseline, LS mean (SE)	−1.61 (0.26)	−1.62 (0.26)	−1.03 (0.23)	−0.90 (0.22)	−1.53 (0.69)	−2.07 (0.67)	−1.93 (0.25)	−1.35 (0.24)
Between-group difference, LS mean (95% CI)	−0.01 (−0.48 to 0.47)		0.13 (−0.45 to 0.70)		−0.54 (−2.46 to 1.37)		0.58 (0.01 to 1.15)	
P value	0.9761		0.6684		0.5631		**0.0448**	
Assessment of motor function using ALSFRS-R limb function score	**PL N = 99**	**ED N = 100**	**ED-PL N = 41**	**ED-ED N = 45**	**PL N = 12**	**ED N = 13**	**PL N = 66**	**ED N = 68**
Baseline, mean (SD)	18.5 (3.3)	18.1 (3.8)	15.0 (4.9)	15.2 (5.8)	11.0 (3.4)	10.5 (5.4)	19.0 (2.7)	19.3 (2.6)
End point, mean (SD)	14.2 (6.2)	14.6 (5.7)	11.4 (5.9)	12.5 (6.6)	7.1 (3.9)	8.1 (6.0)	14.3 (5.0)	16.0 (4.9)
Change from baseline, LS mean (SE)	−4.00 (0.55)	−3.41 (0.55)	−3.80 (0.48)	−2.78 (0.45)	−4.16 (0.78)	−2.66 (0.76)	−5.12 (0.53)	−3.50 (0.51)
Between-group difference, LS mean (95% CI)	0.59 (−0.42 to 1.61)		1.02 (−0.19 to 2.24)		1.50 (−0.69 to 3.68)		1.61 (0.42 to 2.81)	
P value	0.2487		0.0973		0.1706		**0.0087**	
Assessment of motor function using ALSFRS-R respiratory function score	**PL N = 99**	**ED N = 100**	**ED-PL N = 41**	**ED-ED N = 45**	**PL N = 12**	**ED N = 13**	**PL N = 66**	**ED N = 68**
Baseline, mean (SD)	12.0 (0.0)	12.0 (0.0)	11.7 (0.7)	11.6 (1.1)	12.0 (0.0)	12.0 (0.0)	12.0 (0.0)	12.0 (0.0)
End point, mean (SD)	11.3 (1.8)	11.4 (1.4)	11.0 (2.1)	11.0 (2.1)	11.8 (0.4)	10.4 (3.2)	11.5 (1.1)	11.8 (0.6)
Change from baseline, LS mean (SE)	−0.73 (0.24)	−0.67 (0.24)	−0.75 (0.32)	−0.74 (0.30)	−0.32 (0.69)	−1.79 (0.67)	−0.45 (0.13)	−0.16 (0.13)
Between-group difference, LS mean (95% CI)	0.06 (−0.39 to 0.50)		0.01 (−0.79 to 0.81)		−1.47 (−3.40 to 0.45)		0.29 (−0.01 to 0.60)	
P value	0.7950		0.9801		0.1274		0.0593	

ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; CI = confidence interval; ED = edaravone; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error.

Note: ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17.

Note: Efficacy data are reported for the period from the start of cycle 1 to the end of cycle 6 for studies 16, 18, and 19 and the period from the start of cycle 7 to the end of cycle 12 for Study 17.

Note: Continuous outcomes for all studies used LOCF for patients who completed the third treatment cycle and a linear regression model that adjusted for the dynamic allocation factors. The dynamic allocation factors for studies 16 and 17 were: ALSFRS-R score change during the pre-observation period, initial symptom, and concomitant use of riluzole. The dynamic allocation factor for Study 18 was ALSFRS-R score change during the pre-observation period. The dynamic allocation factors for Study 19 were: ALSFRS-R score change during the pre-observation period, El Escorial revised Airlie House diagnostic category, and age (at least or less than 65 years).

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] MCI186-18,[13] and MCI186-19.[14]

Table 11: Limb and Bulbar Norris Scale Scores

	Study 16 FAS		Study 17 FAS		Study 18 FAS		Study 19 FAS	
Assessment of motor function using limb Norris Scale score	**PL N = 97**	**ED N = 95**	**ED-PL N = 41**	**ED-ED N = 44**	**PL N = 12**	**ED N = 12**	**PL N = 63**	**ED N = 68**
Baseline, mean (SD)	52.0 (9.2)	50.8 (10.8)	42.6 (15.2)	42.8 (15.9)	32.1 (12.6)	31.8 (18.8)	52.4 (7.4)	53.2 (7.0)
End point, mean (SD)	40.2 (17.3)	41.5 (16.5)	33.0 (17.6)	35.4 (18.6)	19.2 (12.6)	24.8 (20.6)	39.0 (15.0)	43.2 (14.0)
Change from baseline, LS mean (SE)	−11.35 (1.59)	−9.50 (1.63)	−10.90 (1.34)	−7.37 (1.27)	−13.63 (2.41)	−10.13 (2.41)	−14.91 (1.68)	−11.47 (1.61)
Between-group difference, LS mean (95% CI)	1.86 (−1.11 to 4.82)		3.53 (0.11 to 6.94)		3.50 (−3.38 to 10.38)		3.44 (−0.36 to 7.24)	
P value	0.2178		**0.0430**		0.3022		0.0757	
Assessment of motor function using bulbar Norris Scale score	**PL N = 97**	**ED N = 95**	**ED-PL N = 41**	**ED-ED N = 44**	**PL N = 12**	**ED N = 12**	**PL N = 63**	**ED N = 68**
Baseline, mean (SD)	34.9 (6.6)	33.9 (7.3)	32.2 (9.6)	30.5 (9.9)	37.4 (2.9)	32.1 (7.8)	35.5 (5.1)	34.7 (7.0)
End point, mean (SD)	31.5 (9.1)	30.9 (9.9)	29.6 (11.6)	28.3 (11.1)	33.9 (4.5)	24.5 (14.0)	31.5 (8.9)	32.0 (10.0)
Change from baseline, LS mean (SE)	−4.80 (0.70)	−4.62 (0.72)	– 3.13 (0.71)	−3.47 (0.68)	−4.14 (2.28)	−8.05 (2.28)	−5.89 (0.79)	−4.44 (0.76)
Between-group difference, LS mean (95% CI)	0.17 (−1.13 to 1.48)		−0.34 (−2.15 to 1.47)		−3.92 (−10.42 to 2.59)		1.46 (−0.33 to 3.24)	
P value	0.7925		0.7098		0.2242		0.1092	

ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; CI = confidence interval; ED = edaravone; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; PL = placebo; SD = standard deviation; SE = standard error.

Note: ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17.

Note: Efficacy data are reported for the period from the start of cycle 1 to the end of cycle 6 for studies 16, 18, and 19, and the period from the start of cycle 7 to the end of cycle 12 for Study 17.

Note: Continuous outcomes for all studies used LOCF for patients who completed the third treatment cycle and a linear regression model that adjusted for the dynamic allocation factors. The dynamic allocation factors for studies 16 and 17 were: ALSFRS-R score change during the pre-observation period, initial symptom, and concomitant use of riluzole. The dynamic allocation factor for Study 18 was ALSFRS-R score change during the pre-observation period. The dynamic allocation factors for Study 19 were: ALSFRS-R score change during the pre-observation period, El Escorial revised Airlie House diagnostic category, and age (at least or less than 65 years).

Source: Clinical study reports for studies MCI186-16,[11] MCI186-17,[12] MCI186-18,[13] and MCI186-19.[14]

Harms

Only those harms identified in the review protocol are reported subsequently (Table 3). See Table 12 for detailed harms data.

Adverse Events

In Study 16, at least one AE was reported in 88.5% of patients in the placebo group and 89.2% in the edaravone group. In Study 17, at least 97.8% had at least one AE in the edaravone-placebo group, 91.7% in the edaravone-edaravone group, and 92.0% in the placebo-edaravone group. In Study 18, 100.0% had at least one AE event in the placebo group and 92.3% had at least one AE in the edaravone group. In Study 19, 83.8% had at least one AE in the placebo group and 84.1% in the edaravone group.

Serious Adverse Events

In Study 16, a lower percentage of patients with at least one serious AE (SAE) was reported in the edaravone group (17.6%) than in the placebo group (23.1%). In Study 17, the edaravone-edaravone group had a higher percentage of patients with at least one SAE (52.1%) than did the placebo-edaravone group (44.3%), and the edaravone-placebo group (28.9%). In Study 18, at least one SAE was reported in a higher percentage of patients in the edaravone group (23.1%) than in the placebo group (16.7%). In Study 19, the placebo group reported a higher percentage of patients (23.5%) with at least one SAE than was reported in the edaravone group (15.9%). Across studies, dysphagia was the most commonly reported SAE.

Withdrawal Due to Adverse Events

In Study 16, there was a lower percentage of withdrawals due to AEs (WDAEs) in the edaravone group (2.9%) than in the placebo group (7.7%). In Study 17, the edaravone-edaravone group had a higher percentage of WDAEs (18.8%) than the placebo-edaravone group (9.1%) and the edaravone-placebo group (6.7%). In Study 18, a higher percentage of patients withdrew due to AEs in the edaravone group (7.7%) than in the placebo group (0%). In Study 19, the placebo group reported 2.9% WDAEs, while none were reported in the edaravone group. Across studies 16, 17, and 18, respiratory failure was the most common AE that lead to withdrawal.

Mortality

There were five deaths reported in Study 16: two (2%) in the placebo group and three (3%) in the edaravone group. The five deaths included an additional death that was captured in the survival analysis for death or certain disease progression. In the Study 17 extension, three deaths were reported as part of the survival analysis. An additional three deaths were reported in the safety set, one in the edaravone-placebo group, and two in the edaravone-edaravone group. One death was reported in Study 18 in the edaravone group, which is the same death as the one included in the survival analysis. No deaths were reported in Study 19. Respiratory failure and respiratory-related disorders were the cause of death in all cases except one, where the death was due to cardiac arrest.

Notable Harms

Notable harms related to the method of administration were not considered serious, aside from one SAE caused by a catheter-site infection in the placebo-edaravone group of Study 17. AEs related to injection, infusion, or catheter site were each reported in less than 5% of each group in all the trials. Contusions (categorized under “injury, poisoning, and procedural complications”) were reported in 0% to 19% of each group, though it is not known whether they were related to treatment administration. No severe immunological reactions were reported in the included studies.

Table 12: Harms

	Study 16 Safety Set		Study 17 Safety Set			Study 18 Safety Set		Study 19 Safety Set	
	PL N = 104	ED N = 102	ED-PL N = 45	ED-ED N = 48	PL-ED N = 88	PL N = 12	ED N = 13	PL N = 68	ED N = 69
AEs									
Patients with ≥ 1 AE, N (%)	92 (88.5)	91 (89.2)	44 (97.8)	44 (91.7)	81 (92.0)	12 (100.0)	12 (92.3)	57 (83.8)	58 (84.1)
Most common AEs[a]									
Infections and infestations	38 (36.5)	39 (38.2)	20 (44.4)	21 (43.8)	43 (48.9)	4 (33.3)	3 (23.1)	15 (22.1)	17 (24.6)
Nasopharyngitis	22 (21.2)	22 (21.6)	12 (26.7)	10 (20.8)	28 (31.8)	2 (16.7)	2 (15.4)	5 (7.4)	3 (4.3)
Tinea pedis	1 (1.0)	2 (2.0)	3 (6.7)	3 (6.3)	4 (4.5)	0	1 (7.7)	1 (1.5)	1 (1.4)
Psychiatric disorders	13 (12.5)	9 (8.8)	5 (11.1)	6 (12.5)	13 (14.8)	2 (16.7)	1 (7.7)	5 (7.4)	5 (7.2)
Insomnia	10 (9.6)	9 (8.8)	3 (6.7)	5 (10.4)	7 (8.0)	1 (8.3)	1 (7.7)	4 (5.9)	5 (7.2)
Nervous system disorders	10 (9.6)	15 (14.7)	7 (15.6)	5 (10.4)	11 (12.5)	3 (25.0)	3 (23.1)	11 (16.2)	7 (10.1)
Dyslalia	2 (1.9)	1 (1.0)	1 (2.2)	0	6 (6.8)	0	0	2 (2.9)	1 (1.4)
Headache	3 (2.9)	8 (7.8)	2 (4.4)	1 (2.1)	4 (4.5)	2 (16.7)	3 (23.1)	5 (7.4)	4 (5.8)
Respiratory, thoracic, and mediastinal disorders	14 (13.5)	11 (10.8)	9 (20.0)	17 (35.4)	28 (31.8)	4 (33.3)	6 (46.2)	8 (11.8)	11 (15.9)
Cough	2 (1.9)	1 (1.0)	0	0	5 (5.7)	1 (8.3)	0	0	1 (1.4)
Dyspnea	1 (1.0)	2 (2.0)	3 (6.7)	3 (6.3)	4 (4.5)	0	1 (7.7)	1 (1.5)	0
Upper respiratory tract inflammation	2 (1.9)	1 (1.0)	1 (2.2)	3 (6.3)	4 (4.5)	1 (8.3)	3 (23.1)	2 (2.9)	5 (7.2)
Gastrointestinal disorders	43 (41.3)	32 (31.4)	19 (42.2)	23 (47.9)	48 (54.5)	8 (66.7)	5 (38.5)	19 (27.9)	20 (29.0)
Constipation	17(16.3)	13 (12.7)	8 (17.8)	10 (20.8)	20 (22.7)	0	2 (15.4)	8 (11.8)	8 (11.6)
Diarrhea	5 (4.8)	4 (3.9)	1 (2.2)	3 (6.3)	6 (6.8)	1 (8.3)	3 (23.1)	4 (5.9)	2 (2.9)
Dysphagia	12 (11.5)	8 (7.8)	7 (15.6)	9 (18.8)	22 (25.0)	0	2 (15.4)	10 (14.7)	8 (11.6)
Skin and subcutaneous-tissue disorders	19 (18.3)	22 (21.6)	10 (22.2)	14 (29.2)	28 (31.8)	3 (25.0)	4 (30.8)	16 (23.5)	21 (30.4)
Dermatitis contact	2 (1.9)	3 (2.9)	0	2 (4.2)	2 (2.3)	1 (8.3)	0	3 (4.4)	8 (11.6)
Eczema	2 (1.9)	7 (6.9)	3 (6.7)	3 (6.3)	3 (3.4)	0	0	2 (2.9)	5 (7.2)
Erythema	2 (1.9)	3 (2.9)	3 (6.7)	2 (4.2)	2 (2.3)	1 (8.3)	2 (15.4)	1 (1.5)	1 (1.4)
Pruritus	3 (2.9)	1 (1.0)	1 (2.2)	1 (2.1)	8 (9.1)	1 (8.3)	2 (15.4)	3 (4.4)	0
Musculoskeletal and connective-tissue disorders	24 (23.1)	20 (19.6)	16 (35.6)	10 (20.8)	25 (28.4)	5 (41.7)	2 (15.4)	10 (14.7)	14 (20.3)
Back pain	5 (4.8)	3 (2.9)	2 (4.4)	0	3 (3.4)	1 (8.3)	0	1 (1.5)	4 (5.8)
Myalgia	0	0	0	0	0	2 (16.7)	0	1 (1.5)	4 (5.8)
Muscular disorder	3 (2.9)	3 (2.9)	5	6 (12.5)	12 (13.6)	2 (16.7)	1 (7.7)	1 (1.5)	0

	Study 16 Safety Set		Study 17 Safety Set			Study 18 Safety Set		Study 19 Safety Set	
	PL N = 104	ED N = 102	ED-PL N = 45	ED-ED N = 48	PL-ED N = 88	PL N = 12	ED N = 13	PL N = 68	ED N = 69
			(11.1)						
Muscular weakness	9 (8.7)	7 (6.9)	3 (6.7)	1 (2.1)	5 (5.7)	0	1 (7.7)	1 (1.5)	0
General disorders and administration site conditions	24 (23.1)	30 (29.4)	10 (22.2)	20 (41.7)	36 (40.9)	3 (25.0)	6 (46.2)	10 (14.7)	5 (7.2)
Gait disturbance	16 (15.4)	20 (19.6)	9 (20.0)	14 (29.2)	32 (36.4)	1 (8.3)	4 (30.8)	0	0
Pyrexia	1 (1.0)	1 (1.0)	1 (2.2)	3 (6.3)	2 (2.3)	0	0	3 (4.4)	0
Injury, poisoning, and procedural complications	18 (17.3)	20 (19.6)	13 (28.9)	9 (18.8)	21 (23.9)	3 (25.0)	1 (7.7)	16 (23.5)	18 (26.1)
Contusion	5 (4.8)	12 (11.8)	7 (15.6)	3 (6.3)	8 (9.1)	1 (8.3)	1 (7.7)	9 (13.2)	13 (18.8)
Investigations	10 (9.6)	10 (9.8)	2 (4.4)	3 (6.3)	11 (12.5)	1 (8.3)	1 (7.7)	3 (4.4)	2 (2.9)
Glucose urine present	3 (2.9)	6 (5.9)	0	1 (2.1)	2 (2.3)	0	1 (7.7)	0	0
SAEs									
Subjects with > 0 SAEs, N (%)	24 (23.1)	18 (17.6)	13 (28.9)	25 (52.1)	39 (44.3)	2 (16.7)	3 (23.1)	16 (23.5)	11 (15.9)
Most common SAEs[b]									
Abasia	0	1 (1.0)	0	1 (2.1)	1 (1.1)	0	0	0	0
Bacterial infection	0	0	0	0	0	0	0	1 (1.5)	1 (1.4)
Bladder cancer	0	0	0	1 (2.1)	0	0	0	0	0
Bronchitis	0	0	1 (2.2)	1 (2.1)	0	0	0	0	0
Bronchopneumonia	0	0	0	1 (2.1)	0	0	0	0	0
Cardiac arrest	0	0	0	0	1 (1.1)	0	0	0	0
Catheter-site infection	0	0	0	0	1 (1.1)	0	0	0	0
Colonic polyp	0	0	0	0	1 (1.1)	0	0	0	0
Contusion	0	0	0	0	0	0	0	1 (1.5)	0
Depression	1 (1.0)	0	0	0	0	0	0	1 (1.5)	0
Diverticulitis	0	0	1 (2.2)	0	0	0	0	0	0
Drug-induced liver injury	0	0	0	0	0			1 (1.5)	0
Dysarthria	0	0	1 (2.2)	0	0	0	0	0	0
Dyslalia	2 (1.9)	1 (1.0)	1 (2.2)	0	6 (6.8)	0	0	0	0
Dysphagia	11 (10.6)	8 (7.8)	6 (13.3)	9 (18.8)	22 (25.0)	0	2 (15.4)	8 (11.8)	8 (11.6)
Dyspnea	0	2 (2.0)	2 (4.4)	3 (6.3)	2 (2.3)	0	1 (7.7)	1 (1.5)	0
Enterocolitis	0	0	1 (2.2)	0	0	0	0	0	0
Gait disturbance	2 (1.9)	3 (2.9)	0	4 (8.3)	5 (5.7)	0	1 (7.7)	0	0
Gastric ulcer	0	0	0	0	1 (1.1)	0	0	0	0
Head injury	0	0	0	0	1 (1.1)	0	0	0	0
Hypercapnia	0	0	0	0	1 (1.1)	0	0	0	0
Joint sprain	0	0	0	0	1 (1.1)	0	0	0	0
Lower gastrointestinal hemorrhage	0	0	0	0	0	0	0	1 (1.5)	0
Musculoskeletal disorder	3 (2.9)	3 (2.9)	4 (8.9)	6 (12.5)	10 (11.4)	1 (8.3)	1 (7.7)	1 (1.5)	(0)
Muscular weakness	1 (1.0)	1 (1.0)	0	1 (2.1)	3 (3.4)	0	0	0	0
Pneumonia	0	1 (1.0)	0	1 (2.1)	2 (2.3)	0	0	0	0

	Study 16 Safety Set		Study 17 Safety Set			Study 18 Safety Set		Study 19 Safety Set	
	PL N = 104	ED N = 102	ED-PL N = 45	ED-ED N = 48	PL-ED N = 88	PL N = 12	ED N = 13	PL N = 68	ED N = 69
Pneumonia aspiration	1 (1.0)	0	1 (2.2)	1 (2.1)	1 (1.1)	0	0	2 (2.9)	(0)
Prostate cancer	0	0	1 (2.2)	0	0	0	0	0	0
Pelvic venous thrombosis	0	0	0	0	0	1 (8.3)	0	0	0
Respiratory arrest	0	0	0	0	1 (1.1)	0	0	0	0
Respiratory disorder	0	4 (3.9)	1 (2.2)	2 (4.2)	2 (2.3)	0	0	2 (2.9)	2 (2.9)
Respiratory failure	5 (4.8)	1 (1.0)	2 (4.4)	6 (12.5)	5 (6.8)	0	1 (7.7)	0	0
Retinal vein occlusion	0	0	0	0	1 (1.1)	0	0	0	0
Skin laceration	0	0	0	0	1 (1.1)	0	0	0	0
Speech disorder	0	0	0	0	0	0	0	2 (2.9)	1 (1.4)
Sputum retention	0	1 (1.0)	1 (2.2)	0	1 (1.1)	0	0	0	0
Stomach discomfort	0	0	0	1 (2.1)	0	0	0	0	0
Upper-limb fracture	0	0	1 (2.2)	0	0	0	0	0	0
WDAEs									
WDAEs, N (%)	8 (7.7)	3 (2.9)	3 (6.7)	9 (18.8)	8 (9.1)	0	1 (7.7)	2 (2.9)	0
Most common reasons[b]									
Bronchopneumonia	0	0	0	1 (2.1)	0	0	0	0	0
Cardiac arrest	0	0	0	0	1 (1.1)	0	0	0	0
Dyspnea	0	0	0	1 (2.1)	0	0	0	0	0
Pneumonia	0	0	0	1 (2.1)	0	0	0	0	0
Pneumonia aspiration	0	0	0	0	1 (1.1)	0	0	0	0
Respiratory disorder	0	1 (1.0)	0	1 (2.1)	0	0	0	1 (1.5)	0
Respiratory failure	4 (3.8)	1 (1.0)	2 (4.4)	6 (12.5)	5 (5.7)	0	1 (7.7)	0	0
Rash	0	0	0	0	0	0	0	1 (1.5)	0
Sputum retention	0	0	1 (2.2)	0	0	0	0	0	0
Deaths									
Number of deaths, N (%)	2 (1.9)	3 (2.9)	1 (2.2)	4 (8.3)	1 (1.1)	0	1 (7.7)	0	0
Most common reasons									
Respiratory failure	2	1	2	3	0	0	1	0	0
Respiratory disorder	0	2	0	0	0	0	0	0	0
Pneumonia	0	0	0	1	0	0	0	0	0
Bronchopneumonia	0	0	0	1	0	0	0	0	0
Cardiac arrest	0	0	0	0	1	0	0	0	0
Notable Harms									
General disorders and administration site conditions, N (%)	24 (23.1)	30 (29.4)	10 (22.2)	20 (41.7)	36 (40.9)	3 (25.0)	6 (46.2)	10 (14.7)	5 (7.2)
Injection-site rash	0	0	0	0	0	0	0	1 (1.5)	0
Injection-site reaction	0	1 (1.0)	0	0	0	0	0	2 (2.9)	0
Infusion-site erythema	0	0	0	0	0	0	0	2 (2.9)	3 (4.3)
Infusion-site pain	0	0	0	0	0	0	0	2 (2.9)	3 (4.3)
Infusion-site swelling	0	0	0	0	1 (1.1)	0	0	2 (2.9)	0
Infusion-site phlebitis	1 (1.0)	0	0	0	0	0	0	1 (1.5)	0
Catheter-site dermatitis	0	0	0	0	0	0	0	1 (1.5)	1 (1.4)
Catheter-site inflammation	2 (1.9)	0	0	0	0	0	0	0	0

	Study 16 Safety Set		Study 17 Safety Set			Study 18 Safety Set		Study 19 Safety Set	
	PL N = 104	ED N = 102	ED-PL N = 45	ED-ED N = 48	PL-ED N = 88	PL N = 12	ED N = 13	PL N = 68	ED N = 69
Catheter-site erythema	1 (1.0)	0	0	2 (4.2)	0	0	0	0	0
Catheter-site pain	1 (1.0)	0	0	0	0	0	0	0	0
Injury, poisoning, and procedural complications, N (%)									
Contusion	5 (4.8)	12 (11.8)	7 (15.6)	3 (6.3)	8 (9.1)	0	0	9 (13.2)	13 (18.8)
Immune system disorders, N (%)									
Seasonal allergy	1 (1.0)	0	0	0	2 (2.3)	0	0	0	0

AE = adverse event; ED = edaravone; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: ED-PL refers to the group receiving edaravone in Study 16 and placebo in Study 17. ED-ED refers to the group receiving edaravone in studies 16 and 17. PL-ED refers to the group receiving placebo in Study 16 and edaravone in Study 17.

Note: AEs for Study 17 were reported from the start of cycle 7 to four weeks after the day of last administration for cycle 15, or two weeks after discontinuation. AEs occurring during Study 16 and present at the start of Study 17 were reported separately.

[a] Frequency > 5%.

[b] Frequency > 1%.

Source: Clinical study reports for studies MCI-186-16, MCI-186-17, MCI-186-18, and MCI-186-19.

Discussion

Summary of Available Evidence

Four randomized trials were included in this review. Three of these were double-blind, parallel-group RCTs in patients with ALS randomized (1:1) to edaravone or placebo: Study MCI186-16 (N = 206; referred to here as Study 16), Study MCI186-18 (N = 25; referred to here as Study 18), and Study MCI186-19 (N = 137; referred to here as Study 19). The fourth RCT, Study MCI186-17 (N = 181; referred to here as Study 17), was a parallel-group extension randomized trial in patients who had completed Study 16. Patients at the beginning of Study 16 were randomized (1:1:2) to edaravone in Study 16 and placebo in Study 17 (edaravone-placebo group); edaravone in Study 16 and edaravone in Study 17 (edaravone-edaravone group); or placebo in Study 16 and edaravone in Study 17 (placebo-edaravone group).

Patients in Study 16 had to be categorized as definite ALS, probable ALS, or "probable ALS – laboratory supported" according to the El Escorial revised Airlie House diagnostic criteria, have grade 1 or 2 ALS according to the Japanese ALS severity classification, have an FVC percentage of at least 70%, and be within three years of ALS onset. The inclusion criteria were the same in Study 18 as for Study 16, except that patients had to have grade 3 ALS according to the Japanese ALS severity classification and an FVC of at least 60%. Patients in Study 19 had to be categorized as definite ALS or probable ALS, have grade 1 or 2 ALS, have an FVC of at least 80%, be within two years of ALS onset, and score at least two points on the "handwriting" and "eating motion" items of the ALSFRS-R. In studies 16, 18, and 19, patients had to have a decrease in ALSFRS-R score of one to four points during the 12-week pre-observation period prior to initiation of treatment. In all of these studies, the concomitant use of riluzole was allowed with no change in dose or administration route during the trials, though riluzole therapy could not be initiated during the trials.

The additional extension of Study 19 assessing the safety of edaravone has been summarized in Appendix 5. The long-term safety extension (LTSE) included patients who completed the sixth cycle of treatment in Study 19. All patients in the LTSE received edaravone, and the treatment duration in the LTSE was another six cycles of treatment (cycles 7 to 12) with the same dosing regimen that was used in cycles 2 to 6 in Study 19. In total, 58 patients who received placebo in Study 19 (placebo-edaravone group) and 65 patients who received edaravone in Study 19 (edaravone-edaravone group) received edaravone in the LTSE.

Interpretation of Results

Efficacy

Study 16 was the first phase III trial for edaravone as a treatment for patients suffering from ALS. However, Study 16 failed to demonstrate the superiority of edaravone over placebo (LSM difference = 0.65 [95% CI, −0.90 to 2.19]). A post hoc analysis of Study 16 identified a subgroup of patients in which the change in ALSFRS-R score for edaravone showed a statistically significant improvement over placebo. This subpopulation had the following characteristics at baseline: a disease duration of fewer than two years, a "definite" or "probable" ALS classification according to the El Escorial revised Airlie House diagnostic criteria, an FVC of 80% or greater, and a score of two or greater on all ALSFRS-R items. The post hoc analysis indicated that this subpopulation had fewer patients who showed

minimum ALSFRS-R progression in the placebo arm and thus were more likely to demonstrate the potential effect of edaravone.

Study 19 was conducted using the criteria identified in the post hoc analysis of Study 16 as part of that study's inclusion criteria. It is possible that these inclusion criteria did indeed result in including only patients with a higher probability of demonstrating ALSFRS-R progression in Study 19, as evidenced by the exclusion of 55 patients (29%) in the pre-observation period due to slow ALSFRS-R progression versus 40 (16%) patients excluded in the Study 16 pre-registration period for the same reason. However, when comparing the baseline characteristics between the two studies, we can observe that, on average, patients in Study 19 compared with patients in Study 16 were older, had more regions with signs of UMN and LMN damage (due to the ineligibility of those categorized as "possible ALS" and "laboratory-supported probable ALS"). Also, more patients in Study 19 had initial bulbar symptoms, yet had a shorter disease duration, better respiratory function, and similar mean ALSFRS-R scores. This may potentially indicate that patients in Study 19 were at a unique clinical window where they had been recently diagnosed (as evidenced by disease duration and lung function), but may have had a worse prognosis (as evidenced by age, initial bulbar symptoms, and diagnostic category). Also, we can observe that the SD of the baseline ALSFRS-R score was smaller in Study 19 than in Study 16, indicating a more homogenous population. Study 19 succeeded in demonstrating the superiority of edaravone over placebo in the change of ALSFRS-R score from baseline (LSM difference = 2.49 [95% CI, 0.99 to 3.98]). In addition, the result achieves the established MCID of a 20% change in the slope of decline as determined using a mixed-effects model in a secondary analysis, where the slope of decline in the edaravone-treated group is −0.88 units per cycle (month) compared with −1.35 units per cycle (month) in the placebo group (LSM difference = 0.47 (95% CI, 0.19 to 0.74).

In studies 16 and 19, when examining the main functional domains assessed in the ALSFRS-R, it can be observed that the main effect is present in the limb domain, rather than in the bulbar or respiratory domains. This is further supported by the breakdown of the Modified Norris Scale, where the limb domain showed a greater numerical between-group difference than the bulbar domain in Study 16, and where the bulbar domain lost the statistically significant finding observed in Study 19. Also, we can observe that no clear differences can be observed in the FVC outcome in both studies.

Study 19 does demonstrate the superiority of edaravone compared with placebo in terms of slowing the disease decline as measured through the ALSFRS-R score, and this was supported by the results of the Modified Norris Scale and the ALSAQ-40. However, other outcomes, including grip strength and pulmonary function, did not demonstrate an edaravone-favourable result. While there were numerically fewer certain disease-progression events in the edaravone arm compared with the placebo arm, the number of events and the duration of the study were not sufficient to perform a proper comparative analysis of event-free survival. As such, it is unclear if treatment with edaravone can increase the overall survival and delay respiratory complications in patients suffering from ALS compared with placebo. The extension studies presented by Study 17 and the extension phase of Study 19 offer little to fill this gap, due to the lack of a relevant control group. In addition, except for Study 18, all of the reviewed studies assess the effects of edaravone in patients who had a largely preserved respiratory function (Study 16: ≥ 70% FVC; Study 19: ≥ 80% FVC) and functional independence. Study 18 was a small, brief exploratory trial (N = 25) which was unlikely to have sufficient statistical power to assess the effects of edaravone in only six months. Although Study 16 was powered to detect

differences, it is uncertain whether the lack of statistical significance in the main outcome was due to edaravone's true lack of efficacy in this patient population, or due to factors pertaining to the nature of the ALSFRS-R tool and the heterogeneity of the included population. However, the statistically significant findings in Study 19 in a more homogeneous population suggest that heterogeneity in patients' baseline characteristics and rate of disease progression were major factors.

While most of the studied population were in earlier stages of ALS at baseline, the experts consulted by CDR cautioned against translating the eligibility criteria to clinical practice as a means of identifying an analogous patient population. The El Escorial revised Airlie House diagnostic criteria were considered by the clinical experts to be necessary for standardizing ALS trials, but not useful in clinical practice for assigning a diagnosis to a patient. The clinical experts also highlighted the need to treat patients as early as possible to preserve motor function, as edaravone is a neuroprotective drug and ALS is a neurodegenerative disease, which is not compatible with requiring patients to progress until they show signs of definite or probable ALS, which was part of the inclusion criteria in Study 19. The Japanese ALS severity classification reflects the functional status of a patient as opposed to the presence of UMN and LMN signs and therefore gives complementary information. This classification system was developed for the edaravone trials and is not used in Canadian clinical practice, according to the clinical experts consulted by CADTH. The clinical experts noted there may not be clear divisions between each stage on the Japanese ALS severity classification scale, potentially leading to difficulty in distinguishing between patients in stage 2 who could have been eligible for Study 19 and patients in stage III who were not. Time from disease onset is not a definitive indicator of disease progression due to the variation among patients in rate of progression. The clinical experts stated that almost every ALS patient experiences a window in which they would be eligible for these studies, though in clinical practice patients may not be diagnosed while still within this window.

The eligibility criteria in Study 19 resulted in a patient population with a faster rate of disease progression relative to the patient population in Study 16. Despite the similarity in baseline ALSFRS-R scores between the two studies, the decrease in scores in the placebo group was greater in Study 19 than in Study 16. This trend, combined with the criterion for change in ALSFRS-R score during the pre-observation period, suggests that the evidence for the efficacy of edaravone in patients with very slowly progressing ALS is particularly limited. The projected disease trajectory of patients with ALS, which is assessed in clinical practice according to the clinical experts consulted for this review, could be an important factor in considering which patients would benefit from edaravone therapy.

An important limitation of the included studies was the early discontinuation of some patients, which may potentially bias the observed treatment effects. Specifically, there were imbalances observed between treatment groups in each study with regard to study discontinuations, with greater than 10% of patients discontinuing in some treatment groups. In studies 16 and 19, greater proportions of patients in the placebo groups discontinued, while the opposite was true in studies 17 and 18. The between-group difference was greatest in Study 17, with 15.6% in the edaravone-placebo group and 29.2% in the edaravone-edaravone group discontinuing. Given that LOCF was used for missing data in patients who completed three treatment cycles and that ALS is associated with a steady decline in motor function, the direction of potential bias would have favoured the treatment group with the greater proportion of discontinuations (provided they occurred following the third treatment cycle). If this was the case in studies 16 and 19, the treatment effect would have been biased against edaravone.

A potential limitation to the generalizability of the included studies was the fact that all of the included patients were Japanese. However, the clinical experts consulted for this review were not aware of any factors that would limit the generalizability of the results to the Canadian setting. In addition, we were unable to find evidence in the literature that race or geography was an important factor in ALS prognosis and management.

Harms

Throughout the included studies, infections, infestations, and gastrointestinal disorders were the most commonly reported AEs. Notable harms related to the method of administration were not considered serious, aside from one catheter-site infection SAE in the Study 17 placebo-edaravone group. AEs related to injection, infusion, or catheter site were reported in less than 5% of each group in all the trials. There was no clear congregation of a specific AE in the edaravone arm as opposed to the placebo arm. SAEs were seen as related to the disease, while deaths were due mostly to respiratory-related events that are also commonly seen in patients suffering from ALS. No severe immunological reactions were reported in the included studies; however, the product monograph for edaravone notes that hypersensitivity reactions and cases of anaphylaxis have been reported in spontaneous post-marketing reports on edaravone.

Potential Place in Therapy[2]

Clinical experts consulted by CADTH stated that — given the natural history of ALS, a fatal disease — the unmet needs of ALS patients are colossal. Any drug that slows down disease progression would be welcome, as the benefit of riluzole is marginal, according to the clinical experts. Edaravone has demonstrated benefit in slowing disease progression in a randomized controlled phase III study (Study 19: 33% over six months) and should be considered for the majority of ALS patients with preserved respiratory function and with functional independence. Edaravone appears to be associated with few serious side effects, which also makes it attractive for widespread use in ALS.

The clinical experts noted that in order for Study 19 to show benefit in a short period of time (six months), very strict inclusion criteria were chosen, targeting ALS patients with a clear diagnosis, preserved respiratory function, functional independence, and an average rate of worsening of symptoms.

To avoid misdiagnosis, they therefore excluded “possible ALS” patients as per El Escorial criteria. Practically speaking, “possible ALS” likely represents the earliest stage of ALS for most patients, and those patients should definitely be candidates for edaravone when diagnosed by ALS experts. Also, studies have shown that the vast majority of patients diagnosed with possible ALS are eventually found to have ALS, and patients with possible ALS are included in most clinical trials. In addition, a drug like edaravone with a neuroprotective mechanism should be used as early as possible in a neurodegenerative disease like ALS.

To enter the study, patients had to have a decline of one to four points in their ALSFRS-R score during a three-month observation period. This observation period cannot be replicated in real-life situations and would likely be unethical, as a neuroprotective drug is most beneficial early in the disease course.

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Inclusion criteria also included an FVC of more than 80% without respiratory complaints. Other criteria targeted early-disease patients (less than two years since ALS onset) with grade 1 or 2 ALS according to the Japanese severity scale and scores greater than one on each item of the ALSFRS-R scale.

While the majority of newly diagnosed ALS patients will meet these criteria, early diagnosis is not always possible, as no biomarker exists for ALS. The diagnosis relies on clinical examination, electromyography, and exclusion of other entities, which often delays diagnosis. In that context, patients diagnosed later would likely also benefit from the drug based on its presumed effects on the pathophysiology of ALS, although these patients were excluded from Study 19 because of the strict inclusion criteria.

In practice, edaravone should be offered to almost all patients new diagnosed ALS. Its mode of administration — intravenous infusions for 10 to 14 days per month — is the main barrier for widespread use. Some patients may refuse this invasive therapy or be unable to travel to obtain it if the drug cannot be infused at home. Patients with advanced ALS with severe disability, such as ventilator-dependent patients with very little limb function, are unlikely to benefit from therapy and should not be offered edaravone.

Most patients with ALS who do not fulfill the strict inclusion criteria of Study 19 would likely benefit from the drug early in their disease course based on its presumed mode of action and should be offered the treatment.

Evidence is lacking for several groups of patients, such as those who progress more slowly over several years, or patients with concomitant frontotemporal dementia. Any decision on treatment should be weighed by the clinician after discussion with the patient and family members, acknowledging a lack of data in these circumstances.

Conclusions

Four RCTs evaluating the efficacy and safety of edaravone versus placebo in patients with ALS were included in this CDR systematic review. Two RCTs (Study 16 and Study 19) were confirmatory trials, while one was an extension of Study 16 (Study 17) and one was an exploratory trial (Study 18). Study 19 demonstrated a statistically significant and clinically meaningful decreased rate of decline in the edaravone group compared with the placebo group as measured through ALSFRS-R change from baseline. This result was further supported by nominal statistically significant findings in the secondary outcomes of change in the Modified Norris Scale from baseline and change in HRQoL using the ALSAQ-40. Other outcomes related to respiratory function, strength, and disease severity classification did not show between-group differences. No statistically significant finding was demonstrated in other studies. Throughout the included studies, no specific AE was markedly more concentrated in the edaravone group than in the placebo group, and all causes of death and SAEs can be common manifestations of ALS. Hypersensitivity reactions and cases of anaphylaxis have been reported in spontaneous post-marketing reports on edaravone. However, these reactions were not observed in the included studies.

While edaravone demonstrated efficacy in decreasing the decline of motor function in patients included in Study 19, its effect on survival, respiratory function, and quality of life are unclear. Patients in Study 19 had baseline disease characteristics corresponding to the early stages of ALS and the extent of the effectiveness of edaravone on patients at later stages of the disease is also unclear. Study 16 showed a decreased rate of decline in ALSFRS-R score in the edaravone group versus the placebo group, but the difference was not statistically significant. The lack of statistical significance for the treatment effect may have been due to the broader range in disease characteristics in the Study 16 patients as opposed to a lack of true efficacy, though the evidence is not conclusive.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group responded to the request for input for Radicava (edaravone), the ALS Society of Canada (ALS Canada), though the submission was made in coordination with seven provincial ALS societies. ALS Canada is a registered charity that supports those living with amyotrophic lateral sclerosis (ALS) by investing in research and advocating both federally and provincially for improved support and health care system access for those affected by ALS. Together with provincial ALS societies, they also provide community-based support to people living with ALS. They do not receive any government funding and fund their research and services through donations.

For the completion of this patient input submission, ALS Canada received external support from a public affairs agency hired by the patient group on a fee-for-service basis. The public affairs agency was involved in supporting data collection and analysis, as were internal resources from ALS Canada. In addition, ALS Canada declared the receipt of financial payment over the past two years from the following companies that may have a direct or indirect interest in this drug review: MT Pharma (the manufacturer of the drug under review), Cytokinetics, Innovative Medicines Canada, and AB Science. Financial payment from these companies came in the form of sponsoring the ALS Canada Research Forum scientific conference; the collective value of these sponsorships did not exceed $20,000 in either of the past two years.

2. Condition Related Information

To inform this patient input summary, ALS Canada collected information regarding the disease through a survey and three focus groups. Two of the focus groups were conducted in English and included 22 people in total; the third focus group included two participants and was conducted in French. The intention of the survey was to capture the experiences and opinions of both patients and caregivers affected by ALS to gain a better understanding of living with ALS for Canadians. The survey was provided in both English and French and was open from June 11 to 24, 2018. A total of 574 responses were received (75% English, 25% French) from patients (36.2%), caregivers (31.5%) and individuals who had lost a loved one to ALS (34.8%). Of those who identified their gender, 67.1% were female and 32.4% were male. The age distribution of respondents was as follows: one (0.2%) respondent was younger than 15; 20 (3.5%) were aged 15 to 25 years; 54 (9.4%) were aged 25 to 35 years; 81 (14.1%) were aged 36 to 45 years; 129 (22.5%) were aged 46 to 55 years; 135 (26.7%) were aged 56 to 65 years; and 136 (23.7%) were over the age of 65.

The patient group defines ALS as a terminal disease that affects the communication between the brain and the muscles of the body that are typically controlled at will, which gradually leads to paralysis. According to the patient group's response, the disease is responsible for approximately 1,000 Canadians dying every year. Further, there are approximately 3,000 people in Canada currently living with ALS; however, it is clear from the patient input response that ALS affects the lives of patients and those around them.

There are a variety of symptoms associated with ALS and they worsen as the patient becomes increasingly paralyzed. The deterioration of motor neurons and inability to control the muscles of the body lead to muscular atrophy. This imposes a significant challenge on many tasks that are performed on a daily basis. The muscular atrophy causes muscle

fatigue and discomfort, cramps and twitches, and muscle stiffness and rigidity; all of which were experienced by nearly all patients, according to the input response. Almost all (96.0%) patient responders reported experiencing decreased muscle tone, which impacts the day-to-day life of not only patients, but caregivers, as well. One patient reported having difficulty attending to their hygiene, showering, dressing, and doing their hair, as they cannot lift their arms above their chest. The patient input response noted that several respondents highlighted the increased time and effort required "to do things that were once simple for them." As one patient described, "I have no arm strength, so I can't even carry a coffee in one hand. I can't hold a knife properly so all my food has to be cut into bite-size pieces. It feels like going through life with a 25-pound weight on each arm. Even trying to get my glasses on and off is exhausting." Despite the exhaustion, patients also have trouble sleeping, with 73.7% of respondents reporting insomnia caused by discomfort. In addition, reports of experiencing headaches, stomach problems, itchiness, and both muscle and nerve pain were highlighted by patients.

Problems relating to the effects of the disease on the muscles extend further. Reduced mobility contributes to joint discomfort and stiffness (reported by 86.9% of patients), as well as issues with circulation, which leads to swollen legs and feet (reported by 61.7% of patients). Assistance is often required for everyday tasks such as walking, transitions from sitting to standing and transitions from lying to sitting. The patient input response indicated this has a "significant negative impact on" or "completely changed" the daily lives of 75.5%, 66.4%, and 63.5% of caregivers respectively. The need for assistance is quite demanding for caregivers, who also report having to plan their day around being able to provide that support. Another common consequence of the disease that has a similarly significantly negative impact on both patients and caregivers is the patient's loss of bladder or bowel control. This was reported by 57.1% of patients, who often need help using the toilet (44.6%) and bathing (62.3%). As one patient shared:

"I have community care three times a day to get me up and toileted and sitting in the chair; fed at the middle of my day and either up from a nap or down for a nap and toileted; and at bedtime to get me toileted and dressed [for] bed. I have diapers/pull-ups on all the time as my control is variable and it involves what and when I eat.… I've eliminated a number of foods that can either promote relaxing of my bowels or overwhelming of my bladder."

ALS may lead to issues with breathing as well, as a result of cramping or weakness of the diaphragm. Choking and excess saliva or dry mouth was also experienced by 58.3% and 70.3% of patients, respectively, in addition to problems with eating and drinking properly, leading to reduced food intake and weight loss, as reported by 48.0% of patient respondents. Patients note they are "losing autonomy bit by bit," and described feelings of humiliation due to drooling and challenges with eating and drinking. In more severe cases, a feeding tube may be required, which also affects caregivers and families: "Family dinners changed and I had a hard time eating at the table enjoying a delicious meal while he was fed through a tube. His empty chair at the dinner table was an emptiness like no other — even though he was just in the other room." The progression of the disease also makes communication difficult for patients; 67.4% of patient respondents reported having trouble forming words and projecting their voice. Some patients receive assistance with speaking or typing/writing (44.6% and 49.7% of patient responders, respectively) as a way to help with communication. The loss of one's ability to speak is not only difficult for practical reasons, but also impacts the patient's quality of life. This was highlighted by a patient's response regarding their "inability to call friends and family members, to attend dinners and

parties with friends and to take part in group discussions," which can be isolating. They also expressed difficulty with accurately expressing themselves.

As a result of the various debilitating ways ALS affects one's life, the disease has a significant impact on the mental health of some patients. Based on the patient input response, 63.4% of patients reported experiencing apathy or depressive behaviour and 68.6% had difficulty controlling their emotions at times. Reports of inattention, obsessive or unusual behaviour, and mood changes/frontotemporal dementia symptoms were also reported by 41.1%, 25.1%, and 20.6% of patients, respectively. As was highlighted throughout this section of the patient input summary, the mental health of caregivers is affected as well. Feelings of losing hope, not being able to do enough for their loved ones, and challenges associated with witnessing them progress through the disease were described. One caregiver noted it was "like living on eggshells" and that they were "always on alert for the next thing to happen" and "worried about the effects of the disease, how they were going to manage it all, educating themselves, securing assistive devices, and researching a care home when the time came."

Lastly, the patient group noted that ALS poses a financial burden as well, costing a family between $150,000 and $250,000. The costs associated with the disease are related to having to purchase medical equipment, making home modifications, and transportation to appointments, among other factors. The disease also leaves many patients unable to work and, due to their support needs; caregivers often cannot work either, or have to adjust their work schedules accordingly.

3. Current Therapy Related Information

As per the patient group's response, a cure for ALS does not currently exist and at this time, there is one medication available in Canada designed to extend the survival of those with ALS, which is riluzole. About half (49.8%) of the patient respondents reported using riluzole for the treatment of ALS, and 36.0% of caregivers reported riluzole was used by those they care for. There was mixed feedback regarding the efficacy of riluzole, with some patients describing an improvement in mood and energy, and others noting no improvement at all. Patients also found the drug to be restrictive in some ways, such as only being effective during a certain time period of the disease, and contraindications due to elevated liver enzymes. A few adverse events (AEs) associated with taking riluzole were also reported by patients, such as cramps, diarrhea, feeling sick, and heartburn.

Due to the lack of disease-modifying treatment options, some patients reported the use of off-label drugs, drugs not marketed in Canada (such as Nuedexta, tirasemtiv), as well as stem cell treatments. Alternatively, patients often try to manage their disease through medications to treat symptoms, such as: antidepressants; anti-anxiety and sleeping medications; muscle relaxants and antispasmodics; concentration medications; anti-inflammatory medications; saliva medications; medications to address gastrointestinal upset; respiratory medications; medications to counteract dizziness; medications to improve control over one's bladder/bowels; laxatives; anti-allergic medications; skin medications; anti-fatigue medications; antinauseants; and medications to treat fluid build-up. Treating symptomatically has proven beneficial for patients; however, patients also noted other symptoms that arise as a result of taking multiple medications, such as sleepiness, diarrhea, constipation, fatigue, and mood changes. In some cases, symptoms such as muscle spasms could not be adequately controlled by the maximum daily dose. Another challenge for patients is the difficulty associated with swallowing certain pills. In addition, the patient response indicated that some patients have used medical cannabis as an

alternative treatment for pain, spasms, sleep, and other issues. Chinese tea and turmeric, vitamins, antioxidants, and minerals were also listed as methods of symptom treatment.

Non-medicinal therapy is also important for the management of ALS. Briefly, ALS patients will receive help from speech therapists, occupational therapists, and physiotherapists, as well as specialty or interdisciplinary care for people diagnosed with ALS. Most of the patient respondents (91.4%) reported having access to an ALS specialist or neurologist, and 48.5% to a multidisciplinary care clinic. The major issue with these specialists and services is accessibility for patients, both in terms of travelling to clinics and delays in accessing equipment and devices, allied health services, and home care, and limitations to government-funded programs. All patients make use of a wide range of assistive devices, from wheelchairs to a bilevel positive airway pressure (BiPAP) machine (a non-invasive ventilation support), to assist with challenges associated with mobility and activities of daily living.

In summary, 55.8% of patient respondents reported that their current treatments were not able to control their ALS symptoms, while 21.5% neither agreed or nor disagreed, and 22.7% agreed that their current treatments were able to control their ALS symptoms. The patient input highlighted that they felt this way “because [their current treatments] do not slow down the progression of the disease; the symptoms of ALS only increase,” “the disease continues to do its damage,” and they are “still wasting away.”

4. Expectations About the Drug Being Reviewed

The patient input response indicated that 26 of the patient respondents had experience with edaravone, and an additional 20 caregiver respondents had experience with someone living with ALS who had used edaravone. Clinical trials for this drug have not been conducted within Canada, which is why so few have experience with it. Those who do have experience with edaravone were able to access it from outside of Canada. Based on the survey results, those who are affected by ALS strongly desire medications that are able to “keep the disease at bay.” Symptoms of particular importance identified by the patient group in terms of what they would like controlled include symptoms that affect mobility, communication, muscle weakness, stiffness and atrophy, swallowing, and nerve pain. There was a strong emphasis on the desire to maintain the ability to perform activities of daily living via a new drug, such as the ability to “continue riding, walking, playing golf, travelling, living my life!!!,” “get back to doing the things I enjoy doing,” and “go out more.” Patients also expressed that a medication that was able to slow the progression of the disease would also translate to reduced depression and anxiety, more quality time spent with family and friends, reduced financial hardship, and a range of other benefits related to quality of life.

The majority (69.2%) of patients who had experience with edaravone agreed with the statement that it “better controlled their ALS symptoms than any other treatment they used.” The patient input submission noted that patients reported a variety of benefits associated with taking edaravone, including having more energy, improved mood, greater strength, reduced muscle twitching and stiffness, reduced pain in the arms and legs, clearer speech, less difficulty projecting their voice, and improved bladder control. Five patient respondents also said they believed the medication may have slowed the progression of the disease. Conversely, 23.1% patient respondents reported they neither agreed nor disagreed with the initial statement about improved control of ALS symptoms with edaravone, and 7.7% somewhat disagreed, disagreed, or strongly disagreed. Five patients reported not experiencing any benefit with treatment; two of these patients discontinued treatment for that reason. Similar feedback was provided by caregivers about the drug’s efficacy, with

five of them noting they did not see an improvement. Despite the mixed results about the efficacy of edaravone, 80.1% of patients recommended that it be made available to people with ALS, and 15.4% supported making it available to those who were “likely to benefit.” One (3.8%) patient did not recommend making this drug available.

Just more than one-third of patients (36.0%) said they deviated from the standard infusion schedule, as some patients experienced a reappearance of symptoms during the 14-day period without infusions. Patients reported that they followed alternative recommendations from a neurologist for the infusion schedule, which seemed to regain control of symptoms. Regarding AEs, 84.6% of patients and 70.6% of caregivers reported they did not experience or observe any AEs related to treatment; although it was also noted that it is difficult to differentiate between symptoms of ALS and possible AEs. The following is a list of the AEs that were reported by patients and caregivers: skin inflammation or rash (three patients, two caregivers) infusion-site redness, swelling, bruising, pressure, or pain (two patients, one caregiver); and bruising (one patient, one caregiver). Respiratory disorder, hypoxia, and glycosuria were each reported by one caregiver.

Edaravone is administered intravenously at home, in hospital, or at a combination of hospital, outpatient clinic, and home for 57.7%, 19.2%, and 15.4% of patient respondents, respectively. Two patients (7.7%) received edaravone at another unspecified location. While this overcomes the issue associated with swallowing pills (described earlier), patients and caregivers expressed that accessing the appropriate services to receive the infusions was difficult, inconvenient, costly, and time-consuming. It was cited that, in some situations, nurses refuse to administer the infusion because they are not insured, which also hinders the ability to train the family on how to administer an infusion independently. Alternatively, the cost of administration at a private clinic was reportedly between $125 and $250 per infusion. Some patients reported using a peripherally inserted central catheter (PICC) line or Port-a-Cath, which requires regular daily maintenance and was noted as limiting for caregivers as it “interferes with daily life.” It is also important to note that family caregivers expressed feeling concern and anxiety about having to administer an infusion, fearing they might make a mistake or cause additional problems. This was an additional, emotional challenge for caregivers, as per the patient input response.

Overall, most patients (76.7%) said they would be willing to follow the recommended treatment schedule, which involves daily infusions for 10 to 14 days followed by a 14-day period without infusions, noting that “anything that decreases the impact of the disease — or stops it altogether — was worth it.” For others, the time commitment, travel to access care, additional visitors to their home, and costs were a deterrent. Patients were also asked whether they would try edaravone if it was offered to them, and 81.4% said they would. As one patient mentioned, “this disease is debilitating, and fatal… anything I could do to slow this progression down so I can spend more time with my children would be amazing.” However, this was not the case for all patients, as some stated they would like more information first, and others did not believe it would help or were not interested in the treatment if it would “prolong their lives or their suffering.”

To summarize the expectations patients and caregivers have for edaravone, based on the patient input submission, they are hoping for a drug that will slow down the progression of ALS. The rapid advancement of disease is a challenge for both patients and caregivers, as one caregiver commented, “There was no time to plan in advance and every accommodation was quickly outstripped by need.” Another caregiver expressed that there was little time for patients to “accept and grieve the loss of independence.” Despite the logistical and financial challenges associated with edaravone treatment, most patients are willing to try the treatment in the hope that it will meet their expectations.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 30, 2018
Alerts:	Bi-weekly search updates until November 21, 2018
Study Types:	Randomized controlled trials, Controlled clinical trials
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab .dq	Abstract Candidate term word (Embase)
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm .pt .rn medall	Name of substance word Publication type Case Registry/EC number/Name of substance Ovid database code; MEDLINE ALL (1946-)
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line#	**Search String**
Search#1 Drug + CCT/RCT study filter	
1	(Edaravone* or radicava* or edarabone* or Methylphenylpyrazolon* or Norantipyrine* or Norphenazone* or phenylmethylpyrazolone* or phenyl methyl pyrazolone* or Radicut* or antipyrine nor or antipyrinenor* or demethylphenazone* or phenazone nor or phenazonenor* or mci 186 or mci186* or HSDB-4102 or HSDB4102 or AI3-03557cx or "BRN 0609575" or "C.I. Developer 1" or CCRIS 512 or CCRIS512 or "CI Developer 1" or "Developer Z" or EC 201-891-0 or EINECS 201-891-0 or NCI-C03952 or NSC 12 or NSC12).ti,ot,ab,kf,rn,hw,nm.
2	1 use medall
3	*norphenazone/
4	(Edaravone* or radicava* or edarabone* or Methylphenylpyrazolon* or Norantipyrine* or Norphenazone* or phenylmethylpyrazolone* or phenyl methyl pyrazolone* or Radicut* or antipyrine nor or antipyrinenor* or demethylphenazone* or phenazone nor or phenazonenor* or mci 186 or mci186* or HSDB-4102 or HSDB4102 or AI3-03557cx or "BRN 0609575" or "C.I. Developer 1" or CCRIS 512 or CCRIS512 or "CI Developer 1" or "Developer Z" or EC 201-891-0 or EINECS 201-891-0 or NCI-C03952 or NSC 12 or NSC12).ti,ab,kw,dq.
5	3 or 4
6	5 use oemezd
7	6 not conference abstract.pt.

MULTI-DATABASE STRATEGY	
Line#	**Search String**
8	2 or 7
9	exp animals/
10	exp animal experimentation/ or exp animal experiment/
11	exp models animal/
12	nonhuman/
13	exp vertebrate/ or exp vertebrates/
14	or/9-13
15	exp humans/
16	exp human experimentation/ or exp human experiment/
17	or/15-16
18	14 not 17
19	8 not 18
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
21	Randomized Controlled Trial/
22	exp Randomized Controlled Trials as Topic/
23	"Randomized Controlled Trial (topic)"/
24	Controlled Clinical Trial/
25	exp Controlled Clinical Trials as Topic/
26	"Controlled Clinical Trial (topic)"/
27	Randomization/
28	Random Allocation/
29	Double-Blind Method/
30	Double Blind Procedure/
31	Double-Blind Studies/
32	Single-Blind Method/
33	Single Blind Procedure/
34	Single-Blind Studies/
35	Placebos/
36	Placebo/
37	Control Groups/
38	Control Group/
39	(random* or sham or placebo*).ti,ab,hw,kf,kw.
40	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
41	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
42	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
43	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
44	allocated.ti,ab,hw.
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
46	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
47	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
48	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
49	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
50	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
51	or/20-50
52	19 and 51

MULTI-DATABASE STRATEGY	
Line#	**Search String**
Search#2 Drug + Indication	
53	(Edaravone* or radicava* or edarabone* or Methylphenylpyrazolon* or Norantipyrine* or Norphenazone* or phenylmethylpyrazolone* or phenyl methyl pyrazolone* or Radicut* or antipyrine nor or antipyrinenor* or demethylphenazone* or phenazone nor or phenazonenor* or mci 186 or mci186* or HSDB-4102 or HSDB4102 or AI3-03557cx or "BRN 0609575" or "C.I. Developer 1" or CCRIS 512 or CCRIS512 or "CI Developer 1" or "Developer Z" or EC 201-891-0 or EINECS 201-891-0 or NCI-C03952 or NSC 12 or NSC12).ti,ot,ab,kf,rn,hw,nm.
54	Amyotrophic Lateral Sclerosis/
55	((Amyotrophic adj2 Lateral adj2 Sclerosis) or ALS or Charcot Disease or Gehrig* Disease or Lou Gehrig* or Guam disease).ti,ab,kf.
56	54 or 55
57	53 and 56
58	57 use medall
59	*norphenazone/
60	(Edaravone* or radicava* or edarabone* or Methylphenylpyrazolon* or Norantipyrine* or Norphenazone* or phenylmethylpyrazolone* or phenyl methyl pyrazolone* or Radicut* or antipyrine nor or antipyrinenor* or demethylphenazone* or phenazone nor or phenazonenor* or mci 186 or mci186* or HSDB-4102 or HSDB4102 or AI3-03557cx or "BRN 0609575" or "C.I. Developer 1" or CCRIS 512 or CCRIS512 or "CI Developer 1" or "Developer Z" or EC 201-891-0 or EINECS 201-891-0 or NCI-C03952 or NSC 12 or NSC12).ti,ab,kw,dq.
61	59 or 60
62	Amyotrophic Lateral Sclerosis/
63	((Amyotrophic adj2 Lateral adj2 Sclerosis) or ALS or Charcot Disease or Gehrig* Disease or Lou Gehrig* or Guam disease).ti,ab,kw,dq.
64	62 or 63
65	61 and 64
66	65 use oemezd
67	66 not conference abstract.pt.
68	58 or 67
69	68 not 18
70	52 or 69
71	remove duplicates from 70
56	54 or 55
57	53 and 56
58	57 use medall
59	*norphenazone/
60	(Edaravone* or radicava* or edarabone* or Methylphenylpyrazolon* or Norantipyrine* or Norphenazone* or phenylmethylpyrazolone* or phenyl methyl pyrazolone* or Radicut* or antipyrine nor or antipyrinenor* or demethylphenazone* or phenazone nor or phenazonenor* or mci 186 or mci186* or HSDB-4102 or HSDB4102 or AI3-03557cx or "BRN 0609575" or "C.I. Developer 1" or CCRIS 512 or CCRIS512 or "CI Developer 1" or "Developer Z" or EC 201-891-0 or EINECS 201-891-0 or NCI-C03952 or NSC 12 or NSC12).ti,ab,kw,dq.
61	59 or 60
62	Amyotrophic Lateral Sclerosis/
63	((Amyotrophic adj2 Lateral adj2 Sclerosis) or ALS or Charcot Disease or Gehrig* Disease or Lou Gehrig* or Guam disease).ti,ab,kw,dq.
64	62 or 63
65	61 and 64
66	65 use oemezd
67	66 not conference abstract.pt.

MULTI-DATABASE STRATEGY	
Line#	**Search String**
68	58 or 67
69	68 not 18
70	52 or 69
71	remove duplicates from 70

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	July 2018
Keywords:	Radicava (edaravone), amyotrophic lateral sclerosis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Excluded Studies

Table 13: Excluded Studies

Reference	Reason for Exclusion
Okada M, Yamashita S, Ueyama H, Ishizaki M, Maeda Y, Ando Y. Long-term effects of edaravone on survival of patients with amyotrophic lateral sclerosis. eNeurologicalSci. 2018;11:11-4.[55]	Study design
Takei K, Tsuda K, Takahashi F, Palumbo J. Post-hoc analysis of open-label extension period of study MCI186-19 in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):64-70.[56]	Study design
Writing Group On Behalf Of The Edaravone ALS 19 Study G. Open-label 24-week extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(sup1):55-63.[57]	Study design (described in Appendix 5)
Yoshino H, Kimura A. Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (phase II study). Amyotroph Lateral Scler. 2006;7(4):247-51.[52]	Study design

Appendix 4: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- 40-item Amyotrophic Lateral Sclerosis (ALS) Assessment Questionnaire (ALSAQ-40)
- ALS Functional Rating Scale – Revised (ALSFRS-R)
- Japanese ALS severity classification
- Modified Norris Scale

Findings

Forty-Item Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40)

The ALSAQ-40 is a 40-item, disease-specific questionnaire that was created specifically to assess health-related quality of life (HRQoL) in patients with ALS.[45-47] The questionnaire is composed of five dimensions corresponding to: eating and drinking (3 items), communication (7 items), activities of daily living (ADL)/independence (10 items), mobility (10 items), and emotional well-being (10 items).[45] The questionnaire is completed by patients based on a two-week recall of experiences they may have had, which are rated by frequency of occurrence on a five-point Likert scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always or cannot do at all).[11-14] Each scale is then converted to a summary score from zero (best health status) to 100 (worst health status) by dividing the total raw score of each item by the maximum possible raw score of all scale items then multiplying that by 100.[45] The ALSAQ-40 has also been translated and validated in various languages other than English, including Japanese.[49]

Jenkinson et al. (1999) assessed the ALSAQ-40 for internal validity and reliability in patients diagnosed with ALS.[46] Briefly, 95 patients from the Motor Neurone Disease (MND) Association in England, Wales, and Northern Ireland (MND Association of the UK) were asked to complete a large survey regarding their health at baseline and at a three-month follow-up, which was completed by 74 patients (77.9%). The survey included the ALSAQ-40 and questions related to their general health and the change from baseline. In terms of reliability, Cronbach's alpha statistic was used and determined to be above 0.9 for each dimension of the ALSAQ-40 or above 0.84 when the dimensions were broken down by the patients' global subjective assessment of their health state, indicating an acceptable level (≥ 0.7) of reliability.[58] Construct validity was assessed using the known-groups approach and Kruskal–Wallis test was for comparison. A statistically significant trend across the three groups (poor/fair, good, and very good/excellent) was determined for the following domains, indicating the ability to differentiate between the groups of varying disease severity: eating and drinking ($P < 0.001$), physical mobility ($P < 0.02$), and emotional functioning ($P < 0.001$). The findings for the communications and ADL/independence dimensions were not statistically significant.

An additional study reviewed the ALSAQ-40 in terms of response rate, the completeness of the data at an item level, item-total score correlations, internal consistency, and presence of floor or ceiling effects.[47] This was done by surveying patients who belonged to the MND Association of the UK regarding patient needs and quality of life based on the ALSAQ-40.

Response rates by item were high, with no more than 4.0% of data missing for any item, suggesting that none of the questions were problematic for patients to complete, according to the authors. The questionnaire also demonstrated acceptable internal consistency for most items based on Spearman's ρ, which ranged from 0.61 to 0.92 ($P < 0.001$), as well as internal consistency reliability for each domain score, as each had a Cronbach's α coefficient greater than 0.9.

Lastly, Jenkinson et al. (2003) surveyed members of the MND Association of the UK to determine a minimally clinically important difference (MCID) for the ALSAQ-40.[50] An initial survey containing the ALSAQ-40 was sent out to 1,979 members, followed by a second survey that included the ALSAQ-40 plus five transition questions regarding change since the previous survey. Change was judged by having participants answer if they were "better," "about the same," "a little worse," or "much worse" than three months ago.

Using the 764 [38.6%] surveys that were returned for all five dimensions of the ALSAQ-40, the MCID was calculated based on the mean change score (standard deviation [SD]) for individuals reporting a little change over the previous three months for the following dimensions:

- physical mobility, 3.35 (14.10), $P \leq 0.001$
- ADL/independence, 5.67 (13.28), $P \leq 0.001$
- eating and drinking, 6.40 (20.46), $P \leq 0.001$
- communication, 6.67 (16.52), $P \leq 0.001$
- emotional functioning, 2.67 (15.45), $P \leq 0.02$.

The ALSAQ-40 is limited by the lack of construct validity for the communications and ADL/independence dimensions as well as less-than-acceptable internal consistency (Spearman's $\rho < 0.70$) for six items, four of which correspond to the emotional functioning dimension. The MCID for the ALSAQ-40 was determined using an anchor-based approach, which incorporates the patient's perspective. However, the anchor or questionnaire used to assess a meaningful change in HRQoL for patients was not validated and highly subjective.

ALS Functional Rating Scale – Revised (ALSFRS-R)

The ALSFRS-R is a questionnaire-based scale designed to allow clinicians to quickly measure functionality or physical function regarding ADLs for patients living with ALS.[38-40] The ALSFRS-R is composed of 12 questions that cover four main domains, which are gross motor activity, fine motor activity, respiratory function, and nutrition. More specifically, the topics addressed are: speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, as well as dyspnea, orthopnea, and respiratory insufficiency.[40] The last three concerning respiratory function were an addition to the original ALSFRS, thus creating the revised version. Further, an alternative scale for patients with a gastrostomy is provided for the question concerning cutting food and handling utensils. Each question is scored on a five-point scale from 0 to 4, where 0 = absent function and 4 = no impairment. The score for each question is summed for an overall score ranging from zero to 48. ALSFRS-R is widely used in clinical trials and other patient-oriented research.[59]

The ALSFRS demonstrated test–retest reliability and internal consistency using data collected from three trials: the study that originally validated the ALSFRS; a nine-month placebo-controlled therapeutic randomized controlled trial (RCT) for ALS conducted in 36

centres in the US and Canada; and a phase I and II study that evaluated the biological effect of a treatment for ALS in 279 patients at 21 sites over a six-month period.[39] An overall intraclass correlation coefficient (ICC) of 0.96, 0.95, and 0.94 was determined for each of the studies, respectively.[39] Acceptable test–retest reliability for each item of the ALSFRS was determined using Cohen's kappa (κ), which was greater than 0.76 for all items with the exception of "breathing" for one study where κ = 0.59.

The revised version of the ALSFRS was assessed for validity using data from a clinical trial for brain-derived neurotrophic factor for ALS, which included 387 placebo-treated patients who were evaluated monthly using the ALSFRS-R for nine months.[40] Internal consistency was assessed using Cronbach's alpha, which was greater than 0.67 for each individual item of the scale; however, reliability should be 0.70 or higher. The total ALSFRS-R score did meet the 0.70 threshold with a Cronbach's alpha of 0.73. This study also evaluated the construct validity of the ALSFRS-R by comparing it to the Sickness Impact Profile (SIP), a general assessment of health, as well as the forced vital capacity (FVC) percentage for the respiratory subscale. The ALSFRS-R was well correlated with the SIP (Pearson's correlation coefficient = −0.72), but the correlation with FVC was poor (Pearson's correlation coefficient = 0.40). The author suggested this may be attributed to the subjectivity of the ALSFRS-R compared with an objective FVC measure.[40]

The determination of a clinically meaningful change in the ALSFRS-R was carried out in two studies. The first was a survey of members of the Northeast ALS Consortium (NEALS), i.e., ALS clinical experts, to determine whether a clinically significant change in the slope of ALSFRS-R decline could be agreed upon.[38] A simple survey was sent to 65 experts, which asked them to rate the level of clinical meaningfulness of changes of 10% to 50% (time period not specified) in the ALSFRS-R slope (score versus time) from 1 to 7, where 1 = not very clinically meaningful, 4 = somewhat clinically meaningful, and 7 = very clinically meaningful. Forty-two (65%) surveys were returned. Briefly, a change of 20% to 25% in the slope (time period not specified) of ALSFRS-R was deemed clinically meaningful, as per expert opinion (93% and 100% of ALS experts rated a 20% and 25% decrease, respectively, as at least somewhat clinically meaningful).[38]

Gordon, et al. (2007) also analyzed the performance of outcome measures used in early clinical trials for ALS based on a short-duration (six months), small–sample size (N = 30) trial, to determine if the end points perform as they do in large trials, which end points have the least variability over six months, and whether any could act as surrogates for survival.[41] The smallest clinically meaningful change according to patients was also explored. This was done by asking patients to rate their change from their last visit in terms of physical condition, emotional state, ability to enjoy social life, and overall quality of life. Each question was rated using a visual analogue scale from 1 to 7, where 1 = very much worse, 4 = about the same, and 7 = very much better. The response for each of the four questions was summed for a clinical meaningfulness score (CMS). The CMS was used to reflect patient-perceived clinical change and was also determined to be associated with the ALSFRS-R using a linear mixed-effects model (P = 0.025). Based on this association, the authors reported a one-unit change in the CMS (i.e., in patient-perceived clinical function) corresponding to a nine-point decrease in the ALSFRS-R (95% CI, 8 to 10).

The questions of the respiratory subscale do not correspond well with FVC, which is commonly used to measure respiratory status for ALS patients. Also, the MCID was not derived using one or more formal statistical approaches; rather, it is based on expert opinion and therefore does not necessarily reflect what is clinically meaningful to patients.

Although there was a study that investigated the MCID from the patient and caregiver perspective as well, the results were mainly inconclusive or based on a small sample size. Also of note, the original validation studies were carried out nearly 20 years ago, which may affect the generalizability of the results when applied today, as the standards of care may have changed. Despite this, the FDA supports the use of the ALSFRS-R as a measure of efficacy for ALS treatment and as a demonstration of treatment effect on function in daily living.[51]

Japan ALS Severity Classification

The Japanese ALS severity classification scale was used in the edaravone trials to evaluate the severity of ALS in patients. Patients are assessed by an investigator or sub-investigator using the scale,[11-14] which is based on a rating of the functional ability of patients. The level of functionality is classified into one of five categories on an ordinal scale, with 1 representing the least amount of functional impairment associated with severity of disease, and 5 representing the most. The scales are defined as follows: 1 = able to work or perform housework; 2 = independent living but unable to work; 3 = requiring assistance for eating, excretion, or ambulation; 4 = presence of respiratory insufficiency, difficulty in coughing out sputum or dysphagia; and 5 = using a tracheostomy tube, tube feeding, or tracheostomy positive-pressure ventilation.[11-14] Information regarding the validity and reliability of this outcome or an MCID were not identified.

Modified Norris Scale

The Modified Norris Scale is another tool that is used to evaluate the functional ability of patients with ALS and is composed of two parts.[42] The first is referred to as the Limb Norris Scale, which includes 21 items regarding ADLs related to the extremities, such as “hold up head,” “buttoning, zipping,” and “stand up.”[11-14] The second part, the Norris Bulbar Scale, is composed of 13 items that are used to evaluate bulbar function, or function relating to speech and swallowing.[11-14] Each item is scored on an ordinal four-point scale, corresponding to the following values and ratings or functional scores: normal (3 points), somewhat impaired (2 points), inadequate (1 point), and “cannot do at all” (0 points). Both the Limb Norris Scale and Norris Bulbar Scale are totalled by summing the scores, for a minimum of zero to a maximum score of 63 points and 39 points, respectively.

The Modified Norris Scale was translated to Japanese for use in the edaravone clinical trials.[42] One minor modification was made and additional explanations were added for each item to accommodate the cultural differences between English-speaking and Japanese patients. The Japanese scale was then validated in 23 patients with motor disturbance and rated by two to four neurologists. Cohen’s kappa was used to assess the test–retest reliability of both the limb and bulbar scale, which was ≥ 0.70 for the items of the limb scale and between 0.41 and 1.00 for the items of the bulbar scale. These analyses supported the test–retest reliability of the former scale, as the cut-off for acceptable reliability is 0.70; however, this varied for the bulbar scale. The evaluation of inter-rater reliability also yielded less-than-acceptable values for both the limb scale ($0.60 \leq \kappa \leq 0.83$) and the bulbar scale ($0.26 \leq \kappa \leq 0.81$). The ICC was used to evaluate the reliability of the total score of the two scales, which was found to be acceptable with an ICC of 0.97 (95% CI, 0.95 to 0.99) for the limb scale, and 0.86 (95% CI, 0.73 to 0.93) for the bulbar scale.

In summary, the items of the bulbar scale were not supported by strong evidence of validity; however, the limb scale and total scores were validated. This should be considered when interpreting assessments made with the Modified Norris Scale. In addition, the only

evidence that was identified for the validity of the Modified Norris Scale was for the Japanese version, which was adapted from the English version and used in the edaravone trials. Further, an MCID was not identified for this scale.

Table 14: Summary of Outcome Measures, Evidence of Validity, and MCID

Instrument	Type	Evidence of Validity	MCID	References
ALSAQ-40	A 40-item ALS-specific HRQoL questionnaire composed of five dimension or domains with varying numbers of items that are scored using a 5-point Likert scale. Scores for each domain are calculated by dividing the sum of the corresponding item scores by the maximum possible score for the domain, multiplied by 100. A lower score corresponds to higher HRQoL.	Yes	MCID was calculated for each domain: • physical mobility = 3.35 (SD, 14.10) • ADL/independence = 5.67 (SD, 13.28) • eating and drinking = 6.40 (SD, 20.46) • communication = 6.67 (SD, 16.52) • emotional functioning = 2.67 (SD, 15.45)	Jenkinson 1999[45] Jenkinson 1999[46] Jenkinson 2000[47] Jenkinson 2003[50]
ALSFRS-R	A questionnaire-based scale designed for use by clinicians to measure ADL functionality for patients living with ALS. Composed of 12 questions that cover four main domains (gross motor activity, fine motor activity, respiratory function, and nutrition), questions are scored on a 5-point scale from zero (absent function) to four (no impairment), and each score is summed for an overall score ranging from zero to 48.	Yes	A change of 20% to 25% in the slope of ALSFRS-R was considered clinically meaningful, according to clinical experts. A one-unit change in clinical function corresponded to a 9-point decrease in the ALSFRS-R (*P* = 0.025; 95% CI, 8 to 10), according to patients.	Cedarbaum 1997[39] Cedarbaum 1999[40] Castrillo-Viguera 2010[38] McElhiney 2014[59]
Japan ALS Severity Classification	This is an assessment of the severity of ALS based on functional capacity. It is evaluated by an investigator or sub-investigator according to a 5-point ordinal scale.	No	Unknown	Clinical Study Report[11-14]
Modified Norris Scale	The 21-item Limb Norris Scale and the 13-item Norris Bulbar Scale are used for a functional assessment of ALS patients, with items scored on a 4-point scale. Lower scores correspond to greater functional impairment. Each scale is summed for a total score ranging from zero to 63 points (Limb Norris Scale) 39 points (Norris Bulbar Scale).	Yes (regarding only the reliability of the Japanese version)	Unknown	Oda 1996[42]

ADL = activities of daily living; ALS = amyotrophic lateral sclerosis; ALSAQ-40 = 40-item ALS Assessment Questionnaire; ALSFRS-R = ALS Functional Rating Scale – Revised; CI = confidence interval; HRQoL = health-related quality of life; MCID = minimal clinically important difference; SD = standard deviation.

Source: See references column.

Appendix 5: Summary of Other Studies

Objective

To summarize the results of the long-term safety extension (LTSE) of Study MCI186-19 (Study 19) that evaluated the long-term safety and efficacy of treatment with edaravone in patients with amyotrophic lateral sclerosis (ALS).

Methods

Patients who completed the sixth cycle of treatment in Study 19 were allowed to continue on to the LTSE. All patients in the LTSE received edaravone, and the treatment duration in the LTSE was another six cycles of treatment (cycles 7 to 12) with the same dosing regimen that was used in cycles 2 to 6 in Study 19. In total, 58 patients who received placebo in Study 19 (placebo-edaravone group) and 65 patients who received edaravone in Study 19 (edaravone-edaravone group) received edaravone in the LTSE.

The same outcomes were assessed in both Study 19 and its LTSE, and the collection of efficacy and safety data were performed at the same time points relative to baseline for the LTSE as in Study 19. All of the patients who received edaravone in the LTSE were included in the full analysis set, which was therefore identical to the safety set (Table 16). Summary statistics were reported for the outcomes, and no formal statistical testing between the placebo-edaravone and edaravone-edaravone groups was conducted for the outcomes. Values recorded at the end of cycle 6 were used as the baseline values for the LTSE. There was no imputation of missing data.

Details of patient characteristics at baseline in the Study 19 LTSE are provided in Table 15. Overall, patients in the PL-ED group had worse motor function and disease severity at baseline in the LTSE. There were differences in the placebo-edaravone group versus the edaravone-edaravone group in terms of the proportion of male patients (62.1% versus 56.9%), the mean ALSFRS-R score (34.8 versus 37.8), and the proportion of patients in stage 3 of the Japan ALS severity classification (41.4% versus 32.3%).

Table 15: Baseline Characteristics

	Study 19 Extension (FAS)	
	PL-ED N = 58	**ED-ED N = 65**
Collected in cycle 1 (double-blind period)		
Male, n (%)	36 (62.1)	37 (56.9)
Age in years, mean (SD)	59.7 (10.0)	60.3 (10.4)
Height in cm, mean (SD)	162.7 (8.5)	162.2 (9.5)
Weight in kg, mean (SD)	58.8 (9.4)	58.2 (13.0)
Disease duration in years, mean (SD)	1.07 (0.47)	1.14 (0.47)
Initial symptom classification, n (%)		
Bulbar	11 (19.0)	14 (21.5)
Limb	47 (81.0)	51 (78.5)
ALS diagnosis, n (%)		
Sporadic	56 (96.6)	64 (98.5)
Familial	2 (3.4)	1 (1.5)

	Study 19 Extension (FAS)	
	PL-ED N = 58	ED-ED N = 65
El Escorial revised Airlie House diagnostic criteria, n (%)		
Definite ALS	21 (36.2)	26 (40.0)
Probable ALS	37 (63.8)	39 (60.0)
Japan ALS severity classification, n (%)		
Grade 1	15 (25.9)	22 (33.8)
Grade 2	43 (74.1)	43 (66.2)
ALSFRS-R score, mean (SD)		
Before pre-registration	43.5 (2.2)	43.6 (2.3)
At baseline in cycle 1	41.7 (2.2)	41.9 (2.5)
Concomitant riluzole, n (%)	53 (91.4)	59 (90.8)
Concomitant drugs other than riluzole, n (%)	57 (98.3)	64 (98.5)
Collected in cycle 7 (baseline of active-treatment period)		
ALSFRS-R score		
Mean (SD)	34.8 (5.8)	37.8 (4.9)
Min, Max	19, 45	25, 47
Japan ALS severity classification, n (%)		
Grade 1	5 (8.6)	8 (12.3)
Grade 2	22 (37.9)	27 (41.5)
Grade 3	24 (41.4)	21 (32.3)
Grade 4	7 (12.1)	9 (13.8)
Grade 5	0	0

ALS = amyotrophic lateral sclerosis; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; ED = edaravone; FAS = full analysis set; PL = placebo; SD = standard deviation.

Source: Clinical study report for Study MCI186-19.[14]

Patient disposition is provided in Table 16. In the placebo-edaravone and edaravone-edaravone groups, 31.0% and 18.5% of patients discontinued the study early. The most common reasons were patient decision and reduced respiratory function. Greater proportions of patients in the placebo-edaravone group discontinued than in the edaravone-edaravone group due to patient decision (12.1% versus 9.2%), the need for all-day respiratory support (5.2% versus none), and reduced respiratory function (10.3% versus 6.2%).

Table 16: Patient Disposition

	Study 19 and Extension	
Study 19 DB treatment period	**PL**	**ED**
Completed Study 19, N	60	67
Study 19 extension OL treatment period	**PL-ED**	**ED-ED**
Received assigned treatment, N	58	65
Completed the study, N (%)	40 (69.0)	53 (81.5)
Discontinued from the study, N (%)	18 (31.0)	12 (18.5)
Reason for discontinuation, N (%)		
Patient decision	7 (12.1)	6 (9.2)
Investigator decided: Difficult to continue due to AE	2 (3.4)	1 (1.5)
All-day respiratory support was required	3 (5.2)	0
FVC ≤ 50% and $PaCO_2$ blood gas of ≥ 45 mm Hg	6 (10.3)	4 (6.2)
Investigator decided: Discontinue due to worsening disease	0	1 (1.5)
Full analysis set, N	58	65

	Study 19 and Extension	
Safety, N	58	65

AE = adverse event; DB = double-blind; ED = edaravone; FVC = forced vital capacity; OL = open-label; $PaCO_2$ = partial pressure of carbon dioxide; PL = placebo.

Source: Clinical study report for Study MCI186-19.[14]

Information on treatment adherence in the LTSE is provided in Table 17. Overall, patients in the edaravone-edaravone group were administered more of their planned doses than patients in the placebo-edaravone group. For the placebo-edaravone group versus the edaravone-edaravone group, 60.3% versus 73.8% had 100% adherence and 22.4% versus 10.8% had less than 70% adherence.

Table 17: Treatment Adherence

	Study 19 Extension FAS	
Treatment adherence, N (%)	**PL-ED N = 58**	**ED-ED N = 65**
100%	35 (60.3)	48 (73.8)
≥ 90%, < 100%	4 (6.9)	6 (9.2)
≥ 80%, < 90%	5 (8.6)	3 (4.6)
≥ 70%, < 80%	1 (1.7)	1 (1.5)
< 70%	13 (22.4)	7 (10.8)

ED = edaravone; FAS = full analysis set; PL = placebo.

Source: Clinical study report for Study MCI186-19.[14]

Results

Safety

Detailed information on adverse events (AEs) is provided in Table 18. During the LTSE, 82.8% of patients in the placebo-edaravone group and 81.5% of patients in the edaravone-edaravone group experienced at least one AE. The most common AEs, reported in at least 10% of patients in at least one group, were dysphagia, constipation, and contusion. There were differences in the placebo-edaravone and edaravone-edaravone groups in the incidence of respiratory failure (5.2% versus 1.5%), dysphagia (22.4% versus 9.2%), pruritus (1.7% versus 7.7%), and arthralgia (1.7% versus 6.2%). As respiratory failure and dysphagia are associated with the progression of ALS, the greater proportions of patients with these AEs in the placebo-edaravone group may be related to the baseline imbalances between the groups in ALSFRS-R score and ALS severity classification.

Serious AEs were reported in 39.7% of the placebo-edaravone group and 26.2% of the edaravone-edaravone group. The most common serious AEs (SAEs) included respiratory disorder (6.9% and 6.2% in the placebo-edaravone and edaravone-edaravone groups, respectively), respiratory failure (5.2% and 1.5%), pneumonia aspiration (5.2% and 3.1%), and dysphagia (22.4% and 9.2%).

Withdrawals due to AEs were reported for 5.2% of patients in the placebo-edaravone group and none were reported in the edaravone-edaravone group. The most common reason for withdrawal was respiratory failure, which was reported in two patients. There were deaths in 6.9% of the placebo-edaravone group and 3.1% of the edaravone-edaravone group. The causes of death were respiratory failure (one patient in each group), respiratory disorder

(one patient in each group), pneumonia aspiration (one patient in the placebo-edaravone group), and stress cardiomyopathy (one patient in the placebo-edaravone group).

In terms of notable harms, no AEs of anaphylaxis were reported. AEs specific to the infusion site or puncture site each occurred in 3.4% or less of each group.

Overall, the safety profile in the LTSE was similar to that of Study 19, with no new safety signals.

Table 18: Summary of Adverse Events

	Study 19 Extension Safety Set	
	PL-ED N = 58	**ED-ED N = 65**
AEs		
Patients with ≥ 1 AE, N (%)	48 (82.8)	53 (81.5)
Most common AEs[a]		
Infections and infestations	11 (19.0)	15 (23.1)
Nasopharyngitis	4 (6.9)	6 (9.2)
Nervous system disorders	4 (6.9)	5 (7.7)
Headache	3 (5.2)	1 (1.5)
Respiratory, thoracic, and mediastinal disorders	10 (17.2)	13 (20.0)
Pneumonia aspiration	3 (5.2)	2 (3.1)
Respiratory disorder	4 (6.9)	4 (6.2)
Respiratory failure	3 (5.2)	1 (1.5)
URTI	1 (1.7)	4 (6.2)
Gastrointestinal disorders	27 (46.6)	17 (26.2)
Constipation	8 (13.8)	7 (10.8)
Dysphagia	13 (22.4)	6 (9.2)
Skin and subcutaneous-tissue disorders	9 (15.5)	19 (29.2)
Eczema	2 (3.4)	5 (7.7)
Pruritus	1 (1.7)	5 (7.7)
Musculoskeletal and connective-tissue disorders	8 (13.8)	9 (13.8)
Arthralgia	1 (1.7)	4 (6.2)
Injury, poisoning, and procedural complications	13 (22.4)	14 (21.5)
Contusion	6 (10.3)	6 (9.2)
Wound	2 (3.4)	4 (6.2)
SAEs		
Subjects with > 0 SAEs, N (%)	23 (39.7)	17 (26.2)
Most common SAEs[b]		
Infections and infestations	0	1 (1.5)
Bronchitis	0	1 (1.5)
Psychiatric disorders	1 (1.7)	1 (1.5)
Depression	1 (1.7)	0
Adjustment disorder	0	1 (1.5)
Nervous system disorders	1 (1.7)	2 (3.1)
Speech disorder	1 (1.7)	2 (3.1)
Cardiac disorders	1 (1.7)	0

	Study 19 Extension Safety Set	
	PL-ED N = 58	**ED-ED N = 65**
Stress cardiomyopathy	1 (1.7)	0
Vascular disorders	0	1 (1.5)
Shock	0	1 (1.5)
Respiratory, thoracic, and mediastinal disorders	10 (17.2)	7 (10.8)
Dyspnea	1 (1.7)	1 (1.5)
Pneumonia aspiration	3 (5.2)	2 (3.1)
Respiratory disorder	4 (6.9)	4 (6.2)
Respiratory failure	3 (5.2)	1 (1.5)
Gastrointestinal disorders	13 (22.4)	6 (9.2)
Dysphagia	13 (22.4)	6 (9.2)
Lower gastrointestinal hemorrhage	1 (1.7)	0
Hepatobiliary disorders	0	1 (1.5)
Cholecystitis	0	1 (1.5)
MSK and connective-tissue disorders	2 (3.4)	3 (4.6)
MSK disorder	2 (3.4)	3 (4.6)
General disorders and administration site conditions	0	2 (3.1)
Gait disturbance	0	2 (3.1)
Injury, poisoning, and procedural complications	1 (1.7)	0
Contusion	1 (1.7)	0
WDAEs		
WDAEs, N (%)	3 (5.2)	0
Most common reasons[b]		
Cardiac disorders	1 (1.7)	0
Stress cardiomyopathy	1 (1.7)	0
Respiratory, thoracic, and mediastinal disorders	2 (3.4)	0
Pneumonia aspiration	1 (1.7)	0
Respiratory failure	2 (3.4)	0
Investigations	1 (1.7)	0
Blood pressure increased	1 (1.7)	0
Blood urine present	1 (1.7)	0
Protein urine present	1 (1.7)	0
Deaths		
Number of deaths, N (%)	4 (6.9)	2 (3.1)
Most common reasons		
Respiratory failure	1 (1.7)	1 (1.5)
Respiratory disorder	1 (1.7)	1 (1.5)
Pneumonia aspiration	1 (1.7)	0
Stress cardiomyopathy	1 (1.7)	0
Notable AEs		
Skin and subcutaneous-tissue disorders		
Acne	0	1 (1.5)
Decubitus ulcer	0	1 (1.5)
Dermatitis	0	1 (1.5)
Dermatitis contact	1 (1.7)	3 (4.6)
Eczema, asteatotic	0	2 (3.1)

	Study 19 Extension Safety Set	
	PL-ED N = 58	**ED-ED N = 65**
Excessive granulation tissue	2 (3.4)	1 (1.5)
Rash	0	1 (1.5)
Seborrheic dermatitis	2 (3.4)	
Toxic skin eruption	0	1 (1.5)
Urticaria	1 (1.7)	1 (1.5)
General disorders and administration site conditions		
Infusion-site erythema	1 (1.7)	2 (3.1)
Infusion-site pain	1 (1.7)	0
Infusion-site pruritus	1 (1.7)	1 (1.5)
Infusion-site reaction	2 (3.4)	0
Infusion-site swelling	1 (1.7)	1 (1.5)
Puncture-site swelling	1 (1.7)	0

AE = adverse event; ED = edaravone; MSK = musculoskeletal; PL = placebo; SAE = serious adverse event; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

[b] Frequency > 1%.

Source: Clinical study report for Study MCI186-19.[14]

Efficacy

Results for selected efficacy outcomes are provided in Table 19. Efficacy outcomes were not formally compared between the groups. Motor function, as assessed with the ALSFRS-R score and respiratory function as assessed with FVC, worsened from baseline to the end of treatment in both the placebo-edaravone and edaravone-edaravone groups. The change in mean ALSFRS-R score was similar between the groups, with a change from 34.8 (standard deviation [SD] of 5.8) to 30.8 (SD of 7.7) in the placebo-edaravone group and a change of 37.8 (SD of 4.9) to 34.1 (SD of 7.2) in the edaravone-edaravone group. Mean FVC decreased from 80.80 (SD of 22.46) to 71.82 (SD of 24.17) in the placebo-edaravone group and from 89.26 (SD of 22.98) to 83.94 (SD of 25.00) in the edaravone-edaravone group. During the efficacy assessment period, greater proportions of patients in the placebo-edaravone group than in the edaravone-edaravone group progressed to loss of upper-limb function (10.3% versus 6.9%), use of tube feeding (8.6% versus 3.4%), and loss of useful speech (8.6% versus 6.9%). In contrast, a greater proportion of patients in the edaravone-edaravone group experienced disability of independent ambulation (5.2% versus 3.4%) and tracheotomy (1.7% versus none).

Table 19: Summary of Key Efficacy Outcomes

	Study 19 Extension FAS	
	PL-ED	**ED-ED**
Assessment of motor function using ALSFRS-R score (primary end point from Study 19)		
Baseline	**N = 58**	**N = 65**
Mean (SD)	34.8 (5.8)	37.8 (4.9)
End point	**N = 37**	**N = 51**
Mean (SD)	30.8 (7.7)	34.1 (7.2)
Survival analysis for death or certain disease progression	**N = 58**	**N = 65**
Death or certain disease progression, n (%)		
Death	2 (3.4)	1 (1.7)
Disability of independent ambulation	2 (3.4)	3 (5.2)
Loss of upper-limbs function	6 (10.3)	4 (6.9)
Tracheotomy	0	1 (1.7)
Use of respirator	0	0
Use of tube feeding	5 (8.6)	2 (3.4)
Loss of useful speech	5 (8.6)	4 (6.9)
Assessment of respiratory function using FVC		
Baseline	**N = 58**	**N = 65**
Mean (SD)	80.80 (22.46)	89.26 (22.98)
End point	**N = 36**	**N = 51**
Mean (SD)	71.82 (24.17)	83.94 (25.00)

ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; ED = edaravone; FAS = full analysis set; FVC = forced vital capacity; PL = placebo; SD = standard deviation.

Source: Clinical study report for Study MCI186-19.[14]

Limitations

While the LTSE provided information on the safety of edaravone when administered for up to 48 weeks, it was not possible to determine if any efficacy observed in Study 19 was maintained in the LTSE due to the progressive nature of the disease and the lack of a control group in the LTSE. No conclusions on safety or efficacy could be drawn concerning comparisons between the placebo-edaravone and edaravone-edaravone group; since statistical testing was not performed, there were notable balances between the groups at baseline and there were substantially greater discontinuations in the placebo-edaravone group.

It is possible that the lack of blinding could have affected AE reporting. However, the most common AEs were those related to disease progression as opposed to the notable harms identified in the systematic review protocol.

The baseline characteristics suggested that, on average, patients who had received placebo during Study 19 had more advanced disease at the start of the LTSE than patients who had received edaravone during Study 19. Consistent with this were the greater proportions of patients in the placebo-edaravone group who discontinued during the LTSE due to respiratory failure or an FVC of 50% or less.

Summary

Overall, the safety profile in the LTSE was similar to that of Study 19 with no new safety signals. In terms of notable harms, no AEs of anaphylaxis were reported and AEs specific to the infusion site or puncture site each occurred in 3.4% or less of each group. AEs were reported in 82.8% of patients in the placebo-edaravone group and 81.5% of patients in the edaravone-edaravone group; serious AEs were reported in 39.7% of the placebo-edaravone group and 26.2% of the edaravone-edaravone group; withdrawals due to AEs were reported for 5.2% of patients in the placebo-edaravone group and none in the edaravone-edaravone group; and death occurred in 6.9% of the placebo-edaravone group and 3.1% of the edaravone-edaravone group. The most common AEs were dysphagia, constipation, and contusion, and the most common serious AEs included dysphagia, respiratory disorder, respiratory failure, and pneumonia aspiration. Comparisons could not be made between the groups, as statistical testing was not performed. There were notable balances between the groups at baseline and there were substantially greater discontinuations in the placebo-edaravone group than in the edaravone-edaravone group (31.0% versus 18.5%). It was not possible to determine if any efficacy observed in Study 19 was maintained in the LTSE due to the progressive nature of the disease and the lack of a control group in the LTSE.

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