



Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Australian Public Assessment Report for Radicava

Active ingredient: Edaravone

Sponsor: Teva Pharma Australia Pty Ltd

August 2024

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
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- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AIS	Acute ischaemic stroke
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	Revised ALS Functional Rating Scale
ARTG	Australian Register of Therapeutic Goods
ASA	Australia -specific annex
BSA	Body surface area
CMI	Consumer Medicines Information
DLP	Data lock point
EESP	Efficacy Expected Sub-population
FAS	Full analysis set
LOCF	Last observation carried forward
MND	Motor neuron disease
NOAEL	No observed adverse effect level
PI	Product Information
PopPK	Population PK data
PT	Preferred Term
QTcF	Corrected QT interval using Fridericia's formula
PSUR	Periodic safety update report
RMP	Risk management plan
SAE	Serious adverse event
TEAEs	Treatment emergent adverse events
TGA	Therapeutic Goods Administration
$\Delta\Delta\text{QTcF}$	Placebo-adjusted change from baseline in QTcF

Product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Product name:</i>	Radicava
<i>Active ingredient:</i>	Edaravone
<i>Decision:</i>	Approved
<i>Date of decision:</i>	17 January 2023
<i>Date of entry onto ARTG:</i>	15 February 2023
<i>ARTG number:</i>	375455
<i>, Black Triangle Scheme</i>	Yes
<i>Sponsor's name and address:</i>	Teva Pharma Australia Pty Ltd Level 1, 37 Epping Road, Macquarie Park, NSW 2113
<i>Dose form:</i>	Concentrated injection
<i>Strength:</i>	30 mg/20 mL
<i>Container:</i>	Ampoule
<i>Pack size:</i>	10
<i>Approved therapeutic use for the current submission:</i>	Radicava is indicated in adults with a diagnosis of amyotrophic lateral sclerosis who are independent in activities of daily living with normal respiratory function and where treatment is initiated within two years of disease onset.
<i>Route(s) of administration:</i>	Intravenous infusion
<i>Dosage:</i>	<p>The recommended dosage of Radicava is 60 mg of edaravone (two ampoules) diluted with 100 mL of 0.9% sodium chloride for infusion and administered as an intravenous infusion over a 60-minute period according to the following schedule:</p> <ul style="list-style-type: none">• 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 14-day periods, followed by 14 day drug free periods. <p>For further information regarding dosage, refer to the Product Information.</p>
<i>Pregnancy category:</i>	B3 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other

direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The [pregnancy database](#) must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from [obstetric drug information services](#) in your state or territory.

Product background

This AusPAR describes the submission by Teva Pharma Australia Pty Ltd (the Sponsor) to register Radicava (edaravone) for the following proposed indication:¹

Radicava is indicated for the treatment of amyotrophic lateral sclerosis.

Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease (MND), a progressive, degenerative disease of the central nervous system (CNS) that primarily involves motor neurons (and their supporting astrocytes). Amyotrophic lateral sclerosis is a rare disease, with an estimated prevalence in Australia of 8.7 per 100,000.

The primary neural pathway from the motor cortex to muscle involves two tiers of neurons: cortical neurons in the motor cortex (upper motor neurons, UMN) and neurons in the anterior horn of the grey matter of the spinal cord (lower motor neurons, LMN). Both groups of neurons are affected in ALS, with involvement of the LMN causing atrophy of muscles (amyotrophy) and involvement of the UMN causing sclerosis of the lateral cortical spinal tract. The clinical picture of ALS consists of wasting and fasciculation of muscles, due to LMN involvement, as well as stiffness and spasticity, due to UMN involvement, with weakness resulting from both UMN and LMN involvement.

Involvement of the motor system may be patchy and asymmetrical, especially during the early phases, with variable involvement of the limbs, face, oropharyngeal muscles, axial muscles, and respiratory muscles. The diagnosis requires demonstration of upper and lower motor neuron pathology in multiple body regions, using clinical examination, electromyography and nerve conduction studies, along with exclusion of other potential causes such as spinal cord compression, space-occupying lesions in the central nervous system, and motor neuropathies.

ALS is a fatal condition. Median survival times are usually reported as 2 to 3 years from the diagnosis (or 3 to 4 years from the first onset of symptom), and only approximately 5-10% of ALS patients live over 10 years from onset. Affected patients require increasing support with activities of daily living, with eventual loss of ambulation, feeding, and communication. As the

¹ This is the original indication proposed by the Sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

disease progresses, weakness becomes more severe and widespread, commonly resulting in death from respiratory failure or as a complication of prolonged immobility.

Involvement of other CNS neurons may cause cognitive impairment or other neurological deficits in addition to the progressive weakness, but weakness is the main symptom in all patients. It has been estimated that approximately 20% of individuals with ALS also develop fronto-temporal dementia (FTD), leading to changes in personality and behaviour. A small proportion of patients also develop Parkinsonism.

Latest research suggests that 10-15% of ALS patients have familial ALS, which has been attributed to several different gene mutations, e.g. the mutation of the superoxide dismutase (SOD1) gene is known to cause ALS in humans as well as ALS-like syndromes in animal models.

However, ALS usually occurs as a sporadic disease, the cause of which is unknown but is suspected to involve a combination of genetic and environmental factors. These factors might include physical trauma or exercise, aging and exposure to environmental toxins. Oxidative stress, which can lead to tissue and cell damage, has been implicated in the pathogenesis of ALS, but the extent to which oxidative stress contributes to the disease progression remains unclear.

Current treatment options for ALS

In Australia, the only PBS-listed treatment for ALS is riluzole, which is thought to block the release of glutamate from neurons and thereby reduce excitotoxic damage to motor neurons. Riluzole has been shown to have only a modest survival benefit in ALS. The main study leading to its registration and subsequent meta-analyses suggested that riluzole typically extends survival by 2 to 3 months and increases the chance of an additional year of survival by approximately 9%.

Other treatments for ALS are based on symptom relief and management of complications. These measures include, where appropriate: analgesia, non-invasive and invasive respiratory support, tube feeding, walking aids and wheelchairs, devices to assist communication, treatment of infections, and other elements of supportive and palliative care.

Currently, ALS is an incurable, devastating condition with a very poor prognosis. There is an unmet need for safe and effective treatments for this condition.

Clinical rationale for Radicava use in ALS

Radicava (edaravone) is a free radical scavenger developed as a neuroprotectant. The Sponsor's rationale for developing edaravone for the treatment of ALS is based on protection of neuronal cell damage against high oxidative stress.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

This is the first application to register edaravone in Australia. Radicava (edaravone) was designated as an orphan drug for the treatment of amyotrophic lateral sclerosis on 17 August 2021. The application for registration of Radicava was submitted on 24 September 2021.

Foreign regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status at the time of product registration.

Region	Submission date	Status	Approved indications
Japan	31 March 1998* 15 December 2008#	Approved on 4 April 2001* Approved on 15 January 2010#	<i>Improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischaemic stroke</i>
	29 October 2014**	Approved on 26 June 2015**	<i>Inhibition on progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS)</i>
United States of America	16 June 2016	Approved on 5 May 2017#	<i>Treatment of amyotrophic lateral sclerosis (ALS)</i>
Switzerland	29 August 2017	Approved on 31 January 2019#	<i>Treatment of amyotrophic lateral sclerosis (ALS)</i>
Canada	8 March 2018	Approved on 3 October 2018#	<i>Treatment of amyotrophic lateral sclerosis (ALS)</i>
South Korea†	15 June 2015* 25 June 2015#	Approved on 18 December 2015**	<i>Delaying progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS)</i>
Indonesia	14 November 2019	Approved on 8 July 2020*	<i>Slowing of progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS)</i>
Thailand	18 December 2019	Approved on 8 April 2021*	<i>Delaying progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS) not more than grade 2 with</i>
China	27 February 2019	Approved on 25 July 2019#	<i>Inhibition on progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS)</i>
Malaysia	10 March 2020	Approved on 13 December 2021*	<i>Radicava (edaravone) is indicated to slow the loss of function in patients with amyotrophic lateral sclerosis (ALS)</i>

Region	Submission date	Status	Approved indications
European Union	30 April 2018	Withdrawn on 24 May 2019 [#]	
Singapore	26 April 2019	Withdrawn on 18 August 2020*	

† The product license in South Korea was withdrawn on 29 June 2020 due to high cost of goods.

*Approval of 30 mg/20 mL Ampoule

#Approval of 30 mg/100 mL Bag

Registration timeline

The following table (Table 2) captures the key steps and dates for this submission.

This submission was evaluated under the [standard prescription medicines registration process](#).

The active ingredient with its proposed indication was given [orphan drug designation](#).

Table 2: Timeline for Submission PM-2021-04298-1-1

Description	Date
Designation (Orphan)	17 August 2021
Submission dossier accepted and first round evaluation commenced	1 November 2021
First round evaluation completed	30 March 2022
Sponsor provides responses on questions raised in first round evaluation	29 June 2022
Second round evaluation completed	7 October 2022
Sponsor's notification to the TGA of errors/omissions in evaluation reports	21 October 2022
Delegate's ² Overall benefit-risk assessment and request for Advisory Committee advice	31 October 2022
Sponsor's pre-Advisory Committee response	15 November 2022
Advisory Committee meeting	1 and 2 December 2022
Registration decision (Outcome)	17 January 2023
Administrative activities and registration in the ARTG completed	15 February 2023
Number of working days from submission dossier acceptance to registration decision*	192

*Statutory timeframe for standard submissions is 255 working days

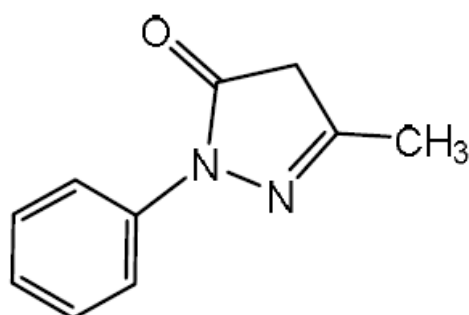
² In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Submission overview and risk/benefit assessment

Quality

The drug product is presented as a 30 mg/20 mL concentrated solution for injection in a Type I clear glass ampoule, packaged in a carton containing 10 ampoules. The concentrated solution must be diluted with 0.9% sodium chloride solution prior to administration by IV infusion.

Figure 1: Structure of edaravone



The drug substance and finished product specifications are acceptable. All Good Manufacturing Practice (GMP) clearances are currently valid and should remain valid for the remainder of this application. The Product Information (PI) is acceptable from a pharmaceutical chemistry perspective.

There is no objection to approval from a pharmaceutical chemistry and quality perspective.

Nonclinical

In vitro, edaravone showed radical scavenging activity, inhibition of lipid peroxidation and protective effects against cell injury in cultured vascular endothelial and neuronal cells, but only at concentrations that exceed the concentrations expected in patients. There was limited efficacy in an animal model of ALS at a dose exceeding that proposed in patients. Overall, the nonclinical studies do not support efficacy in the proposed indication.

No off-target effects were identified in secondary pharmacodynamic studies. Given the margins at the no observed adverse effect level (NOAEL) for safety pharmacology endpoints, no effects on cardiovascular, respiratory, renal or gastrointestinal function are expected in patients with the proposed clinical use.

Overall, the pharmacokinetic profile of edaravone is sufficiently similar in mice, rats, dogs, cynomolgus monkeys and humans to warrant the use of the chosen animal species in toxicity studies. Following intravenous (IV) dosing, terminal elimination half-life values were short in animal species, but slightly longer in humans. The oral bioavailability was low to moderate in mice and in rats. Serum protein binding of edaravone was relatively high in humans, moderate in mice, rats and monkeys and low in dogs. Tissue distribution of drug-related material was generally low in rats. There was evidence of retention of drug-related material (primarily as the product of the reaction of edaravone with radicals). Edaravone is metabolised to two conjugates, glucuronide and sulfate. Both metabolites were seen across animal species and humans and

edaravone sulfate was the predominant circulating drug-related material. Excretion of drug-related material was predominantly via the urine in all animal species and humans.

As multiple enzymes are involved in the metabolism of edaravone and its metabolites, there is a low risk that co-administered drugs will alter edaravone exposures by affecting its metabolism. Co-administered drugs that are organic anion transporter 1 (OAT1) or OAT3 inhibitors may alter exposures to edaravone or its sulfate. Edaravone is not expected to alter the exposure of co-administered drugs that are cytochrome P450 (CYP450) substrates. The conjugated metabolites of edaravone may alter exposures to co-administered drugs that are OAT1 or OAT3 substrates.

Based on data in rats and dogs, edaravone had a low order of acute IV toxicity.

Repeat-dose toxicity studies by the IV bolus route were conducted in rats and dogs (up to 6 months). Edaravone was also studied in multiple short-term repeat-dose studies in rats, dogs and monkeys by continuous IV infusion. Maximum exposures (area under the concentration time curve, AUC) tested were high. Toxicity findings included transient signs of CNS suppression (staggering gait, limpness or sedation) associated with peak plasma levels, nerve degeneration associated with continuous IV infusion, haemolytic anaemia (reduction in red blood cell parameters, increased red blood cell turnover, augmented haematopoiesis, and increase in reticulocytes), and renal toxicity in combination with cephalosporin antibiotic cefalotin (degeneration and necrosis of renal proximal tubule epithelia). When considering the safety margins, the severity of the effects, and the intended patient group who have an impaired blood-brain barrier and nerve damage from the disease, the nerve degeneration seen in animals treated with edaravone should be considered a potential safety concern in patients.

Edaravone was not mutagenic in the bacterial reverse mutation assay or clastogenic *in vitro* (in chromosomal aberration assay in Chinese hamster lung fibroblasts) or *in vivo* (in the mouse micronucleus test). A low genotoxic potential exists for edaravone.

No treatment-related increase in tumour incidence was observed in transgenic mice or rats in 6 month and 2 year, respectively, oral carcinogenicity studies. Edaravone is unlikely to be carcinogenic.

There were no drug-related effects on reproductive organs in male rats treated with edaravone at doses less than or equal to 30 times the clinical dose based on body surface area (BSA). There was a decrease in copulation index and prolonged/irregular oestrus in female rats. The NOAEL for effects on oestrous cycling in female rats was low (3 times the clinical dose based on BSA). Edaravone was not teratogenic in rats or rabbits. Adverse embryofetal development effects (lower fetal weights in rats and increased incidence of embryofetal deaths in rabbits) occurred at maternotoxic doses. High levels of drug-related material were excreted in the milk of lactating rats. In a peri-/postnatal study in rats, findings in the F1 generation included: delayed development in females, increased locomotor activity in behavioural assays, and an increased incidence in embryonic death in the F2 generation. The no adverse effect level for F1 development was subclinical based on BSA.

Injection site reactions are not predicted based on limited animal data.

Withdrawal, place preference and self-administration studies of edaravone in rats, mice and monkeys did not indicate signs for dependence.

The conclusions and recommendations of the nonclinical evaluation are:

- *In vitro* pharmacology studies support that edaravone is a radical scavenging agent. However, overall, the data do not support clinical treatment of ALS with edaravone.

- The retention of drug-related material to arterial tissues is a concern, though no obvious findings in toxicity studies could be attributed to this.
- Findings in the repeat-dose toxicity studies indicates the following as potentially clinically relevant safety concerns:
 - Central nervous system depression if given as an IV bolus injection.
 - Nerve degeneration with lameness.
 - Renal toxicity if used in conjunction with cephalosporin antibiotics; as the mechanism is unknown, edaravone may potentiate the renal toxicity of some other drugs, which cannot be predicted at this stage.
- Edaravone is non-genotoxic and does not pose a carcinogenic hazard.
- Based on the nonclinical data, there are some concerns regarding the registration of edaravone for the proposed indication: limited evidence of efficacy and a potential risk of drug-associated nerve damage. If there was clear evidence of efficacy in clinical studies, the potential risks may be acceptable.

Clinical

Summary of clinical studies

The clinical dossier for edaravone (also referred to as MCI-186) included:

- Five Phase I pharmacokinetic (PK) studies in healthy subjects (three studies in Japan, two studies in Europe):
 - Study MCI-186-01 (Japan): first-in-human study to assess the safety and PK of edaravone, using a single-dose phase and a multi-dose phase.
 - Study MCI-186-14 (Japan): safety and PK of edaravone with a 48-hour continuous infusion.
 - Study MCI-186-E01 (Europe) and Study MCI-186-E02 (Europe): safety and PK of edaravone in Caucasian subjects.
 - Study MCI-186-10 (Japan): PK and pharmacodynamics (PD) of edaravone, and the effect of age on PK.
- Four post-marketing PK or PD studies:
 - Study MCI-186-E05 (Europe): open label, single dose PK study in subjects with severe hepatic impairment compared to subjects with normal hepatic function.
 - Study MCI-186-J22 (Japan): open label, single dose PK study in subjects with mild or moderate renal impairment compared to subjects with normal renal function.
 - Study MCI-186-J23 (Japan): multicentre, open label, single dose PK study in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function.

- Study MCI-186-J25 (Japan): randomised, single blind, placebo controlled, three-way crossover study to evaluate the effect of MCI-186 at therapeutic and supra-therapeutic doses on QT/QTc in healthy subjects.³
- Five efficacy and safety studies in patients with ALS:
 - Study MCI-186-12: Phase II exploratory, proof-of-principle study.
 - Study MCI-186-16: Phase III study (this was a negative study, but post hoc analyses after data unblinding suggested a benefit in a sub-population)
 - Study MCI-186-19: Phase III study (evaluated efficacy in a restricted population based on the post hoc findings from Study MCI-186-16)
 - Study MCI-186-17: extension study for patients enrolled in Study MCI-186-16.
 - Study MCI-186-18: exploratory study in patients with ALS severity grade 3.
- Eight studies of edaravone in patients with acute ischaemic stroke and three studies in patients with subarachnoid haemorrhage were included in the safety evaluation.

Pharmacology

Pharmacokinetics (PK)

The development program included five Phase 1 PK studies in healthy subjects, including three studies (MCI-186-01, MCI-186-14, MCI-186-10) in male Japanese subjects (age range 20 to 71 years, weight 50.9 to 85.0 kg) and two studies (MCI-186-E01, MCI-186-E02) in Caucasian males and females (age range 51 to 77 years, weight 49.9 to 100.3 kg). The studies evaluated different dosing regimens with different doses and infusion durations, ranging from single dose infusions given over 40 minutes to continuous infusions for 48 hours (Table 3). The only PK/PD study directly assessing the proposed dose was MCI-186-J25, a post-marketing QT study in Japanese healthy volunteers. The PK properties of edaravone, as summarised below, are derived primarily from simulation results from Population PK data (popPK) analysis of the five Phase 1 PK studies.

Absorption

Edaravone is administered by intravenous injection with the maximum plasma concentration (C_{max}) of edaravone reached by the end of the infusion (60 mg edaravone for 60 min). No gender effect on edaravone pharmacokinetics has been found. There were no significant racial differences in C_{max} and the AUC of edaravone between Japanese and Caucasian subjects. There was a trend of more than dose-proportional increase in AUC and C_{max} of edaravone. With multiple-dose administration, edaravone does not accumulate in plasma.

³ The QT interval is the time from the start of the QRS wave complex (in an ECG) to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

Table 3 Studies contributing to the PK and PD evaluation of edaravone

Study name	Subjects	Objective	Number of subjects (number per group)	Treatment	Approximate dose/day ^a	Administration period	Demographics			Creatinine clearance/ mL/min median (min-max)	
							Sex	Age range/ years	Body weight/ kg		
PK studies MCII86-01 ^b	Japanese healthy adults	First-in-man study to evaluate safety and PK	42 (7 per group: 5 edaravone, 2 placebo)	I: 0.2 mg/kg/40 min	12 mg	Single dose 1 day	Males only	I: 31.4 ± 5.6 (27-41)	I: 64.1 ± 7.6 (57.8-76.2)	NR	
				II: 0.5 mg/kg/40 min	30 mg			II: 30.7 ± 6.0 (26-43)	II: 63.6 ± 4.6 (58.3-72.8)		NR
				III: 1.0 mg/kg/40 min	60 mg			III: 29.4 ± 5.0 (25-39)	III: 64.7 ± 6.8 (55.2-73.6)		NR
				IV: 1.5 mg/kg/40 min	90 mg			IV: 32.0 ± 5.5 (27-43)	IV: 69.9 ± 7.9 (62.5-85.0)		NR
				VI: 2.0 mg/kg/3 hr	120 mg			VI: 32.0 ± 6.4 (24-44)	VI: 66.8 ± 7.9 (53.7-80.0)		NR
				V: 1.0 mg/kg/40 min/day	60 mg			V: 27.6 ± 2.2 (24-30)	V: 66.6 ± 4.6 (60.8-72.3)		NR
						Multiple dose 7 days					

Study name	Subjects	Objective	Number of subjects (number per group)	Treatment	Approximate dose/day ^a	Administration period	Demographics			Creatinine clearance/ mL/min median (min-max)
							Sex	Age range/ years	Body weight/ kg	
PK studies										
MCI186-14 ^b	Japanese healthy adults	To evaluate safety and PK with slow continuous infusion to support treatment for subarachnoid hemorrhage	8 ^c	48-hr continuous infusion 120 mg/day	120 mg ^d	Single dose 2 days	Males only	23.3 ± 3.1 (20-28)	64.1 ± 8.9 (50.9-75.4)	NR
MCI186-E01 ^b	Caucasian healthy adults	To evaluate safety, tolerability, and the PK profile of edaravone with continuous infusion using high dose	24 (12 per group; 10 edaravone, 2 placebo)	6-hr continuous infusion, A: 0.1 mg/kg/hr 6-hr continuous infusion, B: 0.3 mg/kg/hr	48 mg 144 mg	Single dose 1 day	12 male 12 female	62.42 ± 7.60 (52-75)	71.30 ± 11.91 (49.9-95.0)	A: 75.3 (54.4-97.5) B: 83.2 (62.9-117.4) P: 73.8 (68.5-80.7)

Study name	Subjects	Objective	Number of subjects (number per group)	Treatment	Approximate dose/day*	Administration period	Demographics mean ± SD (min-max)			Creatinine clearance/ mL/min median (min-max)
							Sex	Age range/ years	Body weight/ kg	
PK studies										
MCI186 -E02 ^b	Caucasian healthy adults	To evaluate safety, tolerability, and the PK profile of edaravone and its metabolites	46* (14 per group; 10 edaravone, 4 placebo)	C1:0.1 mg/kg bolus for 3 min +	487 mg	Single dose 1 day	21 males 25 females (51-77)	61.3 ± 9.94 5.5 (58.4-100.3)	71.94 ± 9.94 (58.4-100.3)	NR
				0.25 mg/kg/hr for 23 hr						
				C2:0.2 mg/kg bolus for 3 min +						
				0.5 mg/kg/hr for 23 hr						
MCI186 -10 ^b	Japanese healthy adults and elderly subjects	To evaluate PK and PD of edaravone. To evaluate the effect of age on PK	14 (7 per group; 5 edaravone, 2 placebo)	0.5 mg/kg/30 min ×2 times/day	60 mg	Multiple dose 2 days	Males only	Elderly 68.1 ± 2.1 (65-71) Adult 28.6 ± 3.5 (25-34)	Elderly 92.9 ± 15.2 (70.5-111.6) Adult 113.1 ± 15.7 (93.8-137.8)	
PK /PD study										

Distribution

Edaravone is bound to human serum proteins (92%), mainly to albumin, with no concentration dependence in the range of 0.1 to 50 micromol/L.

Metabolism

Edaravone is metabolised to a sulfate conjugate and a glucuronide conjugate, which are not pharmacologically active. The glucuronide conjugation of edaravone involves multiple uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A6, UGT1A9, UGT2B7, and UGT2B17) in the liver and kidney. In human plasma, edaravone is mainly detected as the sulfate conjugate, which is presumed to be formed by sulfotransferases.

Excretion

In Japanese and Caucasian healthy volunteers, edaravone was excreted mainly in the urine as its glucuronide conjugate form (70-90% of the dose). Approximately 5-10% of the dose was recovered in the urine as sulfate conjugate, and only 1% of the dose or less was recovered in the urine as unchanged form. *In vitro* studies suggest that sulfate conjugate of edaravone is hydrolysed back to edaravone, which is then converted to the glucuronide conjugate in the human kidney before excretion into the urine.

The mean terminal elimination half-life of edaravone is 4.5 to 6 hours. The half-lives of its metabolites are 2 to 2.8 hours.

Renal impairment

Study MCI-186-J22 evaluated the PK of edaravone following a single IV infusion of 30 mg over 60 minutes in subjects with mild or moderate renal impairment compared to subjects with normal renal function. There was no clinically significant impact of mild or moderate renal impairment on the PK of edaravone, so no dose adjustment is proposed for these patients.

Hepatic impairment

Study MCI-186-J23 evaluated the PK of edaravone in subjects with mild or moderate hepatic impairment, and Study MCI-186-E05 evaluated the PK of edaravone in subjects with severe hepatic impairment, compared to subjects with normal hepatic function. Following a single IV infusion of 30 mg over 60 minutes, there was no clinically significant impact of mild, moderate or severe hepatic impairment on the PK of edaravone, so no dose adjustment is proposed for these patients.

PK interactions

The submission did not include clinical drug-drug interaction (DDI) studies. The DDI potential of edaravone was investigated in *in vitro* studies.

Population PK data (popPK)

PopPK analyses were presented based on data from the five Phase 1 PK studies in healthy subjects: MCI-186-01, MCI-186-14, and MCI-186-10 in male Japanese subjects (age range 20 to 71 years, weight 50.9 to 85.0 kg) and MCI-186-E01 and MCI-186-E02 in Caucasian males and females (age range 51 to 77 years, weight 49.9 to 100.3 kg). The Sponsor used the model to investigate covariate effects on PK parameters by race (Japanese vs Caucasian), gender (Caucasian males vs Caucasian females), weight, and age. The analyses showed no effects of gender, age, or weight on any PK parameters. Race had a minor effect on the peripheral volume of distribution 2 (V₂) but was not statistically detected as a covariate for any other PK parameter. Simulations of virtual ALS populations receiving 60 mg/60 min QD for 14 days predicted similar C_{max} and AUC for Japanese and Caucasian subjects.

Pharmacodynamics (PD)

Study MCI-186-10 was primarily a PK study, but lipid peroxide and free fatty acid concentrations in blood were assessed as PD endpoints to investigate the effect of edaravone as a free radical scavenger. There was no significant or meaningful change in lipid peroxide levels in response to therapy. Free fatty acid levels showed an age-related difference but there was no significant change in response to therapy. No PD effect of edaravone was demonstrated in this study.

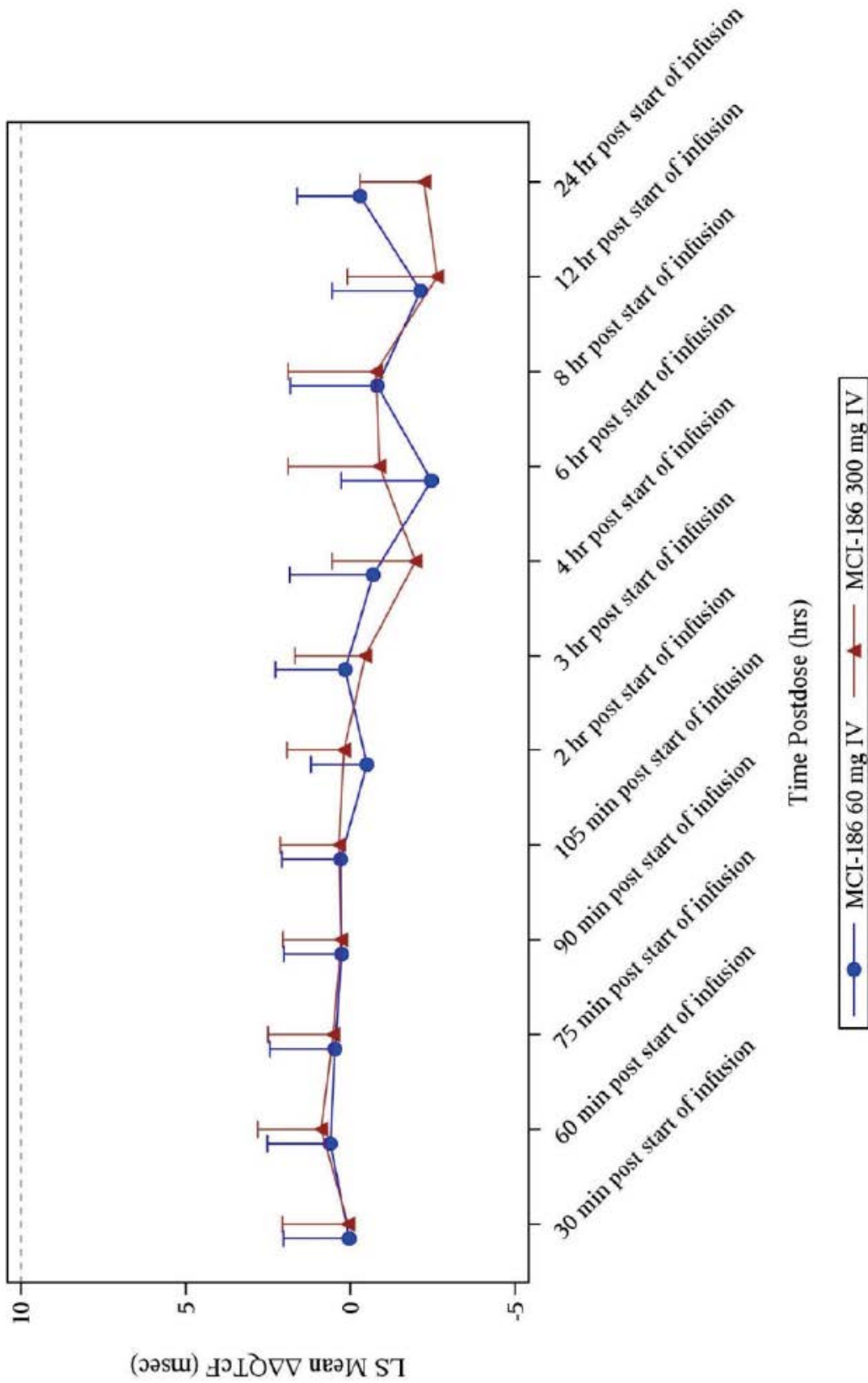
Study MCI-186-12 was an exploratory clinical efficacy study (without a placebo control) that included an assessment of 3-nitrotyrosine (3NT) levels in CSF as a minor PD endpoint. The 3NT biomarker is thought to reflect oxidative stress, and CSF 3NT levels are typically elevated in ALS patients relative to healthy controls. The study showed a nominally significant decline in 3NT from baseline in the 60 mg group, but not in the 30 mg group. The clinical significance of elevated 3NT levels in ALS subjects is unknown, and it is also unknown whether a treatment that lowers 3NT levels is likely to have a meaningful impact on the underlying disease process. The role of 3NT as a surrogate efficacy marker remains uncertain.

QT

The effect of edaravone on the QT interval was evaluated in a post-marketing QT study, MCI-186-J25. It was a randomised, single-blind, placebo-controlled, three-way crossover study of 27 healthy Japanese male subjects. Study drug (edaravone 60 mg, edaravone 300 mg, or placebo) was administered as a single IV infusion over 60 minutes. The primary objective was to evaluate the effect of edaravone on the QT interval corrected for heart rate using Fridericia's formula (QTcF). Secondary objectives were to evaluate the PK profile of edaravone, to evaluate the effect of edaravone on other 12-lead ECG intervals, and to evaluate safety and tolerability.

The study showed no evidence of a significant QT effect from edaravone, even at the supratherapeutic dose of 300 mg. The upper bounds of the 2-sided 90% CIs (equivalent to 1-sided 95% upper confidence bounds) of $\Delta\Delta\text{QTcF}$ were all < 10 msec at the geometric mean C_{max} for each dose level (Figure 1). PK parameters were consistent with the Phase 1 PK studies, and there were no new safety concerns.

Figure 2. Mean Placebo-Adjusted Change from Baseline in QTcF and 1-Sided Upper 95% Confidence Bounds (msec), Study MCI-186-J25



Dose selection

There was no placebo-controlled dose-ranging study to inform dose selection for the efficacy studies in patients with ALS. Instead, the Sponsor adapted the doses used in acute ischaemic stroke (AIS) (30 mg by IV infusion twice a day for 14 days), modifying the regimen for long-term use by using a daily infusion of 60 mg and adding treatment breaks. The dosage regimen evaluated in the Phase 3 studies and proposed for registration is 60 mg administered as an IV infusion daily for 14 days followed by 14 days of no treatment (initial 28-day treatment cycle), and then daily for 10 of the first 14 days of each subsequent 28-day treatment cycle. Consequently, no treatment is administered on 18 days of each subsequent treatment cycle. The treatment breaks appear to have been included for logistical convenience, as there is not a clear pharmacological reason for interrupting treatment.

Study MCI-186-12

This was a Phase 2 exploratory proof-of-principle study that assessed the efficacy and safety of edaravone at two different doses using an open-label, non-randomised, ascending dose design without a placebo control. In this small study, with only 19 subjects evaluable for efficacy, the first five subjects were allocated a dose of 30 mg/day, and subsequent patients received 60 mg/day, with each dose administered as an IV infusion at a rate of 1 mg/min. The first cycle of treatment was for 14 days followed by 14 days of no treatment, and subsequent cycles consisted of treatment for 5 days a week for 2 weeks, followed by a 2-week period with no treatment. Subjects were treated for a total of 6 cycles.

The inclusion criteria were broader than the subsequent Phase 3 studies, with most ALS patients eligible if they could be hospitalised for 2 weeks to receive the study treatment under observation.

The primary efficacy endpoint was change in Revised ALS Functional Rating Scale (ALSFRS-R) score, and other efficacy variables included changes in manual muscle testing, respiratory function testing, arterial blood gas, and CSF/blood parameters. The ALSFRS-R is a disease-specific rating scale that was developed to measure the degree of functional impairment in patients with ALS based on 12 aspects of physical function: Speech, Salivation, Swallowing, Handwriting, Cutting food and handling utensils, Dressing and hygiene, Turning in bed and adjusting bed clothes, Walking (and leg movement), Climbing stairs, Dyspnoea, Orthopnoea, and Respiratory insufficiency (requirement for assisted ventilation). Each function is scored from 4 (normal) to 0 (no ability), with a maximum total score of 48 and a minimum total score of 0. The ALSFRS-R is a validated rating scale that is widely accepted by ALS experts and has been shown to correlate with objective measures of disease status and level of disability. Use of the ALSFRS-R (in conjunction with survival endpoints) is explicitly encouraged by the Committee for Medicinal Product for Human Use (CHMP) guideline. Functional decline averages about 1 point per month in untreated patients and a 20-25% change in the slope of the ALSFRS-R decline is usually considered clinically meaningful.

The primary efficacy endpoint, the ALSFRS-R score, was analysed at each treatment cycle with regression analysis and paired t-tests and is summarised in Table 4. The rate of decline in ALSFRS-R prior to treatment was compared with the rate of decline during treatment (from baseline until 2 weeks after Cycle 6), and subjects with a progression rate $\leq 50\%$ of the initial rate were considered to have had their disease “suppressed” (Table 5).

Table 4 ALSFRS-R Decline on Edaravone Compared to Six months Pre-treatment, Study 12

Open-label Edaravone group (N excluding withdrawals)	Total ALSFRS-R			Summary statistics			
	6 months before start of treatment (mean)	Start of treatment (Baseline) (mean)	6 months after start of treatment (mean)	Change from 6 months before start of treatment to Baseline ^a (mean)	Change from Baseline to end of Cycle 6 ^b (mean)	Degree of suppression 6 months after start of treatment ^c (mean ± SD)	Paired t-test
30 mg (N=4)	39.3	32.0	27.0	-7.3	-5.0	2.3 ± 3.9	P=0.337
60 mg (N=12)	42.7	38.0	35.8	-4.7	-2.3	2.4 ± 3.5	P=0.035

^a Baseline minus 6 months before the start of treatment.

^b End of Cycle 6 minus Baseline.

^c (End of Cycle 6 minus Baseline) minus (Baseline minus 6 months before the start of treatment).

Table 5 “Suppression” of ALSFRS-R Decline by Dose, Study 12

Administration group	Rating			
	Suppression	Fair suppression	No change	Suppression rate
30 mg group	1	3	1	20.0%
60 mg group	7	1	6	50.0%

The results suggested that ALSFRS-R scores declined at a lower rate while subjects were on edaravone than in the 6 months prior to treatment; however, in the absence of a placebo group, it is uncertain whether the change in slope of the ALSFRS-R vs time curve represents an efficacy signal. The efficacy results with edaravone 60 mg were numerically better than with 30 mg, but there was no formal comparison, and patient numbers in the 30 mg group were low.

Efficacy

Efficacy studies included the exploratory Phase 2 Study MCI186-12 (summarised above) and four Phase 3 studies, listed below. The first confirmatory study, Study 16, failed to show a therapeutic benefit, but *Post hoc* analyses of Study 16 after data unblinding identified a sub-population with favourable outcomes. Efficacy in that restricted population was evaluated in the second confirmatory study, Study 19.

- **Study MCI186-16** (Study 16), first confirmatory study in patients with Grade 1-2 ALS.
- **Study MCI186-19** (Study 19), second confirmatory study designed to assess efficacy in a restricted population based on the favourable *post hoc* sub-population from Study 16.
- **Study MCI186-17** (Study 17), an extension study of Study 16.
- **Study MCI186-18** (Study 18), an exploratory study in patients with Grade 3 ALS.

The ALSFRS-R was the major efficacy endpoint in the key efficacy studies.

ALS severity was graded according to the Japan ALS severity scale:

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.

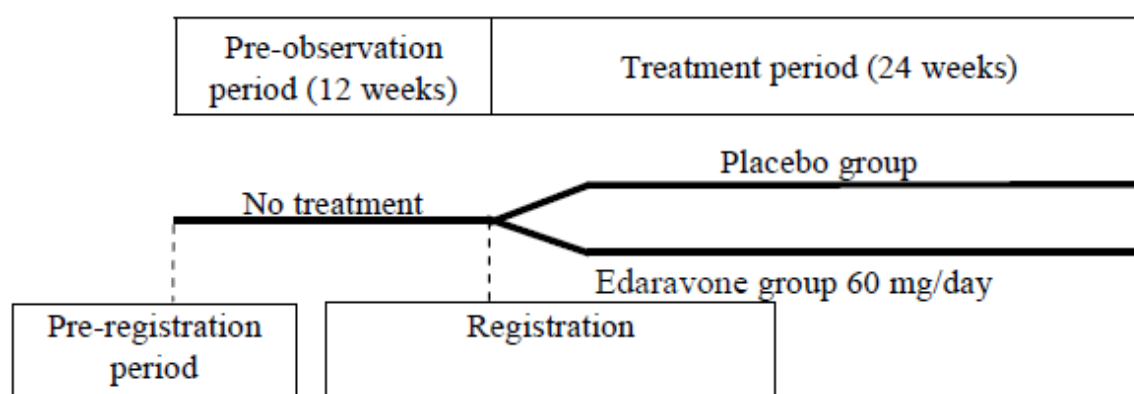
Study MCI186-16 (Study 16)

Study 16 was a double-blind, parallel-group, placebo-controlled, Phase 3 study of edaravone for the treatment of ALS. It was the initial Phase 3 study designed to confirm the efficacy of edaravone in the proposed indication. The study was conducted in multiple centres in Japan between 8 May 2006 and 9 September 2008.

The primary objective was to compare the efficacy of edaravone to placebo in patients with ALS based on change in ALSFRS-R over 24 weeks after treatment initiation. The safety of edaravone in ALS patients was also examined.

The study included a 12-week pre-observation period followed by a 24-week double-blind treatment period (Figure 2). Study treatment was edaravone 60 mg or matching placebo, administered intravenously over 60 minutes, according to the following schedule over six 4-week cycles: daily for 14 days at the start of Cycle 1, and then daily for 10 of 14 days at the start of each subsequent 4-week cycle. No treatment was administered on 14 days in Cycle 1 and 18 days in each subsequent cycle. Use of riluzole was permitted at a stable dose.

Figure 3 Outline of Study design, Study 16



Inclusion criteria were:

- Patients who correspond to “definite ALS,” “probable ALS,” or “probable ALS-laboratory supported” by the El Escorial revised Airlie House diagnostic criteria.
- Patients with ALS severity grade 1 or 2 by the Japan ALS severity classification
- Patients whose % forced vital capacity (%FVC) is 70% or higher.
- Patients who are within 3 years after the onset of ALS at written informed consent
- Patients between 20 and 75 years old at written informed consent
- Patients who gave written informed consent to study participation
- Patients whose ALSFRS-R score changed by -1 to -4 points during the 12-week pre-observation period.⁴

A sample size of 100 subjects in each group was planned based on a treatment effect of 2.2 points on ALSFRS-R which would provide 95% power when the standard deviation (SD) is 4.3, 85% power when the SD is 5.2, and 67% power when the SD is 6.5.

246 patients gave informed consent and underwent pre-registration, and 206 patients were randomised to treatment in the double-blind treatment period. Subjects were randomised 1:1 (102 to edaravone and 104 to placebo), with dynamic allocation based on 3 factors: ALSFRS-R score changes during the 12-week pre-observation period (-1, -2 vs -3, -4), initial symptom

⁴ This criterion was established because it was considered difficult to evaluate efficacy in patients with rapid progression or no change in disease status.

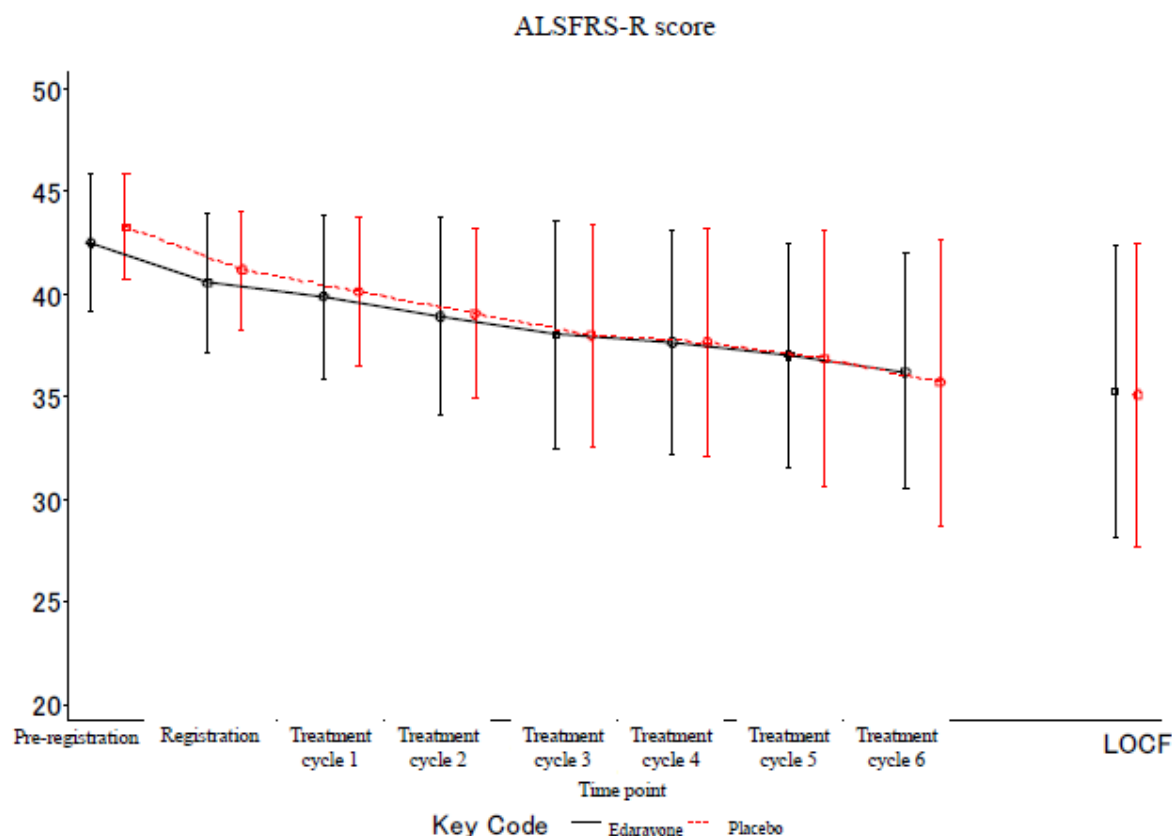
(bulbar symptoms vs limb symptoms), and concomitant use of riluzole (Yes or No). 205 patients were included in the full analysis set (FAS; 101 edaravone, 104 placebo), so the study was adequately powered under its initial assumptions. Baseline demographic characteristics and disease data were reasonably balanced between the treatment groups.

The primary efficacy endpoint was the change in ALSFRS-R from baseline in Cycle 1 to the end of Cycle 6 or at discontinuation. Secondary endpoints were: time to death or certain disease progression (disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator and use of tube feeding), domain-specific ALSFRS-R score, %FVC, Modified Norris Scale score, ALS Assessment Questionnaire (ALSAQ40) score, grip strength, pinch grip strength, and ALS severity classification.

The FAS was used for primary analysis. The evaluator highlighted concerns that two analytical methods were specified for the primary analysis without applying any correction for multiplicity of methods. The secondary endpoints were not formally ranked, and the multiplicity of secondary endpoints was not discussed in the study report.

The study failed to achieve its primary endpoint. The change (mean \pm SD) in ALSFRS-R from baseline in treatment cycle 1 to the end of treatment cycle 6 or at discontinuation was -5.3 ± 5.4 points in the edaravone group and -6.0 ± 6.0 points in the placebo group (Figure 3). Both of the analysis methods specified for the primary analysis failed to demonstrate a significant treatment effect (Table 6, Table 7), so the concern regarding a lack of correction for multiplicity of methods for the primary analysis is not of particular relevance. A range of prespecified sensitivity analyses in the FAS also failed to show a significant treatment effect, and results in the Per Protocol Set were consistent with the FAS.

The secondary efficacy endpoints did not support a therapeutic benefit with edaravone compared to placebo. The study did not show a meaningful benefit for time to death or certain disease progression (Table 8, Table 9), bulbar component of the ALSFRS-R score (Table 10), limb component of the ALSFRS-R score (Table 11), respiratory component of the ALSFRS-R score (Table 12), %FVC (Table 13), Modified Norris Scale score (Table 14), ALSAQ40 (Table 15), grip strength (Table 16), and pinch-grip strength (Table 17). There was a small numerical trend favouring edaravone for change in ALS severity classification, but there were missing data and no statistical analysis was performed.

Figure 4 ALSFRS-R score (mean \pm S.D.), FAS, Study 16**Table 6 Analysis of changes in ALSFRS-R score from baseline in Treatment cycle 1 to 2 weeks after the end of Treatment cycle 6, last observation carried forward (LOCF), FAS, Study 16**

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-6.35 \pm 0.84	0.65 \pm 0.78	<i>t</i> = 0.82	<i>P</i> = 0.4108
Edaravone	-5.70 \pm 0.85	(-0.90, 2.19)		

Table 7 Repeated measures analysis of variance of ALSFRS-R score, FAS, Study 16

Group	Adjusted mean	Between-group difference in the adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% CI)	<i>t</i> -value	<i>P</i> -value
Placebo	37.43 \pm 0.46	0.65 \pm 0.44	<i>t</i> = 1.48	<i>P</i> = 0.1415
Edaravone	38.08 \pm 0.47	(-0.22, 1.52)		

Table 8 Death or certain disease progression; number of events (FAS), Study 16

Event	Placebo	Edaravone	Total
Death	2	2	4
Disability of independent ambulation	23	28	51
Loss of upper limbs function	4	2	6
Tracheotomy	2	0	2
Use of respirator	3	1	4
Use of tube feeding	3	5	8

Table 9 Survival analysis on death or certain disease progression (FAS), Study 16

ALSFRS-R score changes during pre-observation period	Group	n	No. of events*	Between-group comparison	
-4, -3	Placebo	32	14	$P = 0.3814$ (Stratified log-rank test)	
	Edaravone	29	12		
-2, -1	Placebo	72	13		$P = 0.3992$ (Stratified generalized Wilcoxon test)
	Edaravone	72	20		

* Death, disability of independent ambulation, loss of upper arm function, tracheotomy, use of respirator, and use of tube feeding. In patients who experienced multiple events, the day of onset of the first event was defined as the day of event.

Table 10 Changes in ALSFRS-R score (bulbar function) from baseline in Treatment Cycle 1 to the end of Treatment Cycle 6 (LOCF, FAS), Study 16

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-1.61 \pm 0.26	-0.01 \pm 0.24 (-0.48, 0.47)	$t = -0.03$	$P = 0.9761$
Edaravone	-1.62 \pm 0.26			

Table 11 Changes in ALSFRS-R score (limb function) from baseline in Treatment Cycle 1 to the end of Treatment Cycle 6 (LOCF, FAS), Study 16

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-4.00 \pm 0.55	0.59 \pm 0.51 (-0.42, 1.61)	$t = 1.16$	$P = 0.2487$
Edaravone	-3.41 \pm 0.55			

Table 12 Changes in ALSFRS-R score (respiratory function) from baseline in Treatment Cycle 1 to the end of Treatment Cycle 6 (LOCF, FAS), Study 16

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-0.73 \pm 0.24	0.06 \pm 0.23 (-0.39, 0.50)	$t = 0.26$	$P = 0.7950$
Edaravone	-0.67 \pm 0.24			

Table 13 Changes in %FVC from baseline in Treatment Cycle 1 to the end of Treatment Cycle 6 (LOCF, FAS) (Unit: %), Study 16

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-17.49 \pm 2.39	2.92 \pm 2.24 (-1.49, 7.33)	<i>t</i> = 1.31	<i>P</i> = 0.1928
Edaravone	-14.57 \pm 2.41			

Table 14 Changes in Total Norris Scale score from baseline in Treatment Cycle 1 to the end of Treatment Cycle 6 (LOCF, FAS), Study 16

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-16.15 \pm 2.00	2.03 \pm 1.89 (-1.69, 5.75)	<i>t</i> = 1.08	<i>P</i> = 0.2835
Edaravone	-14.12 \pm 2.05			

Table 15 Changes in ALSAQ40 score from baseline in Treatment Cycle 1 to the end of Treatment Cycle 6 (LOCF, FAS), Study 16

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	19.13 \pm 3.79	0.48 \pm 3.50 (-6.44, 7.39)	<i>t</i> = 0.14	<i>P</i> = 0.8921
Edaravone	19.60 \pm 3.82			

Table 16 Changes in Grip Strength score from baseline in Treatment Cycle 1 to the end of Treatment Cycle 6 (LOCF, FAS), Study 16

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-5.71 \pm 0.69	0.89 \pm 0.64 (-0.37, 2.16)	<i>t</i> = 1.39	<i>P</i> = 0.1650
Edaravone	-4.81 \pm 0.69			

Table 17 Changes in Pinch-Grip Strength score from baseline in Treatment Cycle 1 to the end of Treatment Cycle 6 (LOCF, FAS), Study 16

Group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm S.E.	LSMean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-1.03 \pm 0.15	0.20 \pm 0.14 (-0.08, 0.48)	<i>t</i> = 1.39	<i>P</i> = 0.1653
Edaravone	-0.83 \pm 0.15			

Subgroup analyses were conducted on the FAS for the primary endpoint based on sex, age, duration of disease, initial symptom, El Escorial revised Airlie House diagnostic criteria, ALS severity classification, concomitant use of riluzole, complications, and ALSFRS-R score changed during the pre-observation period. Some subgroups showed greater numerical difference than the overall cohort, but no subgroup achieved nominal significance for the primary endpoint.

Post hoc analyses after data unblinding were conducted which identified sub-populations with more favourable results than the prospective FAS. The Sponsor uses the term “Efficacy Expected Sub-Population” (EESP) for the sub-population defined by removing two groups of patients from the FAS:

- Patients with any parameters of ALSFRS-R score ≤ 1 at baseline in Treatment Cycle 1.
- Patients with %FVC $< 80\%$ at baseline in Treatment Cycle 1.

During the *post hoc* analysis, the Sponsor considered that further enrichment would be necessary to facilitate measurement of a treatment effect on disease progression, removing two more sets of patients with unfavourable data:

- Patients with ALS who did not meet “definite or probable ALS” criteria according to the El Escorial revised Airlie House diagnostic criteria.
- Patients with onset of ALS symptoms more than 2 years prior.

The rationale for the *4-factor* restricted population (referred to as *definite or probable/EESP/2y*) was that it would be necessary to exclude stable patients who would be unlikely to show disease progression during the 24-week study period. The *definite or probable/EESP/2y* population was considered to have high likelihood for progression of the disease as they were diagnosed as having definite or probable ALS and had reached the certainty of that diagnosis within 2 years of initial symptom onset.

The *EESP* comprised 104 patients (54 in the edaravone group and 50 in the placebo group). The *definite or probable/EESP/2y* comprised 72 patients (40 in the edaravone group and 32 in the placebo group), representing only 35% of the 206 patients randomised to treatment in the main study.

The *post hoc* analyses of the primary endpoint in the *EESP* and *definite or probable/EESP/2y* sub-populations are summarised in Table 18. The analyses showed nominal significance for the *EESP* and *definite or probable/EESP/2y* sub-populations. Conversely, the non-*EESP* and non-*definite or probable/EESP/2y* sub-populations trended towards negative (i.e. adverse) treatment effects with edaravone compared to placebo.

Table 18 Difference in ALSFRS-R between Baseline in Cycle 1 and the End of Cycle 6 (LOCF) for Study MCI186-16 (FAS, EESP, Definite-or-Probable/EESP/2y)

Study number	Group	Number of subjects in LOCF analyses	Adjusted mean	Between-group differences in the adjusted mean	p-value
			LS mean \pm SE	LS mean \pm SE (95% CI)	
MCI186-16 (FAS)	P group	99	-6.35 \pm 0.84	0.65 \pm 0.78 (-0.90 , 2.19)	p=0.4108
	E group	100	-5.70 \pm 0.85		
MCI186-16 (EESP) ^a	P group	46	-7.06 \pm 1.13	2.20 \pm 1.03 (0.15 , 4.26)	p=0.0360
	E group	53	-4.85 \pm 1.24		
MCI186-16 (Definite or Probable/EESP/2y) ^a	P group	29	-7.59 \pm 1.34	3.01 \pm 1.33 (0.35 , 5.67)	p=0.0270
	E group	39	-4.58 \pm 1.55		
MCI186-16 (non-“EESP”) ^a	P group	53	-5.24 \pm 1.25	-1.42 \pm 1.16 (-3.73 , 0.89)	p=0.2251
	E group	47	-6.65 \pm 1.17		
MCI186-16 (non-“Definite or Probable/EESP/2y”) ^a	P group	70	-5.54 \pm 1.08	-0.57 \pm 1.00 (-2.55 , 1.41)	p=0.5711
	E group	61	-6.11 \pm 1.03		

Note: LOCF was applied to subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.

^a EESP, Definite or Probable/EESP/2y, Non-EESP, and Non-Definite or Probable EESP/2y analyses were post-hoc.

The *post hoc* findings from Study 16 are considered hypothesis-generating (i.e. should not be viewed as providing evidence of efficacy) as the selection of these sub-populations after data unblinding was influenced by known efficacy outcomes. A subsequent Phase 3 study, MCI-186-19, evaluated efficacy in a population based on the *definite or probable/EESP/2y* criteria.

Study MCI-186-19 (Study 19)

This was a Phase III, multi-centre, randomised, double-blind, placebo-controlled, parallel-group study of edaravone for the treatment of ALS. The primary objective was to investigate the efficacy of edaravone 60 mg versus placebo in terms of change in ALSFRS-R score at 24 weeks of treatment. This study evaluated efficacy in a restricted population based on the *post hoc* findings from Study 16. The key features of the study population were that they had relatively mild ALS (Grade 1 or 2) with normal respiratory function, they were enrolled within 2 years of disease onset, and they exhibited intermediate disease progression during a 12-week pre-treatment period. The study was conducted in Japan between 28 November 2011 and 3 September 2014.

The study included a 12-week pre-treatment observation period, a 24-week, double-blind period involving treatment with edaravone or matching placebo as scheduled over six 4-week cycles, and a 24-week active treatment period where all subjects were treated with open-label edaravone as scheduled over six 4-week cycles (Figure 4). Study treatment was edaravone 60 mg diluted with saline, or matching placebo, administered by intravenous infusion over 60 minutes. Treatment was administered once daily for the first 14 days of Cycle 1, and then once daily for 10 days of the first two weeks in each subsequent cycle. Consequently, no treatment was administered for 14 days of Cycle 1, and for 18 days of each subsequent cycle (Figure 5).

Figure 5 Study Design, Study 19

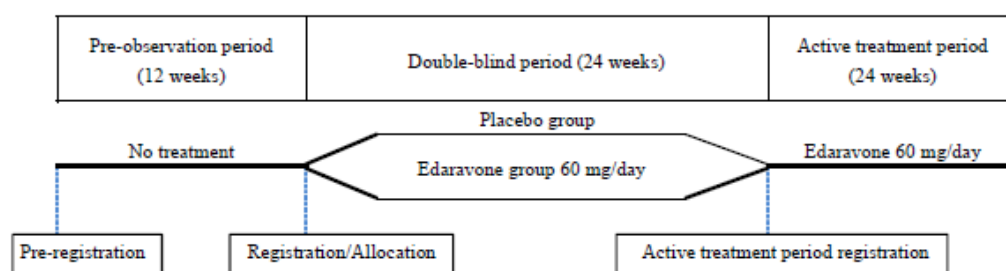


Figure 6 Summary of treatment periods, Study 19

Informed consent	Eligibility check	Pre-registration	Pre-observation period 12 weeks	Registration	Treatment period: double-blind period											
					Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
					Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free
14 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days			

Transition to active treatment period	Treatment period: active treatment period												
	Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		
	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment
10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days

The inclusion criteria were:

1. Patients who are categorised as either "Definite ALS" or "Probable ALS" in the El Escorial revised Airlie House diagnostic criteria.
2. Patients at Grade 1 or 2 in Japan ALS severity classification.
3. Patients scoring ≥ 2 points on each single ALSFRS-R item ("*4. Handwriting*" and "*5. Eating motion*" should be scored ≥ 2 points on each side).
4. Patients with normal respiratory function (%FVC $\geq 80\%$).
5. Patients with ALS that occurred within 2 years at the time of written informed consent.
6. Patients aged 20 to 75 years at the time of giving written informed consent.
7. Patients who provided written informed consent to participate in the present study.
8. Patients in whom changes in ALSFRS-R score during the 12-week pre-observation period are -1 to -4 points.

The inclusion criteria align with the *definite or probable/EESP/2y* sub-population identified from *post-hoc* analyses in Study 16. Use of riluzole was permitted provided the dosage and administration were not changed, but it could not be initiated during the study.

Based on *post hoc* analysis of Study 16, the study planned to recruit 128 subjects (64 per group). Of 213 patients who provided informed consent, 192 were registered and 137 patients were randomised 1:1 to edaravone (n=69) or placebo (n=68) with dynamic allocation based on:

- change in ALSFRS-R score between baseline in the pre-observation period and completion of the pre-observation period (-1 or -2 vs -3 or -4)
- El Escorial revised Airlie House diagnostic criteria (definite vs probable)
- age (≥ 65 vs < 65 years).

127 patients completed the study, 67 in the edaravone group and 60 in the placebo group. Discontinuation was more common in the placebo group (11.8%) than in the edaravone group (2.9%).

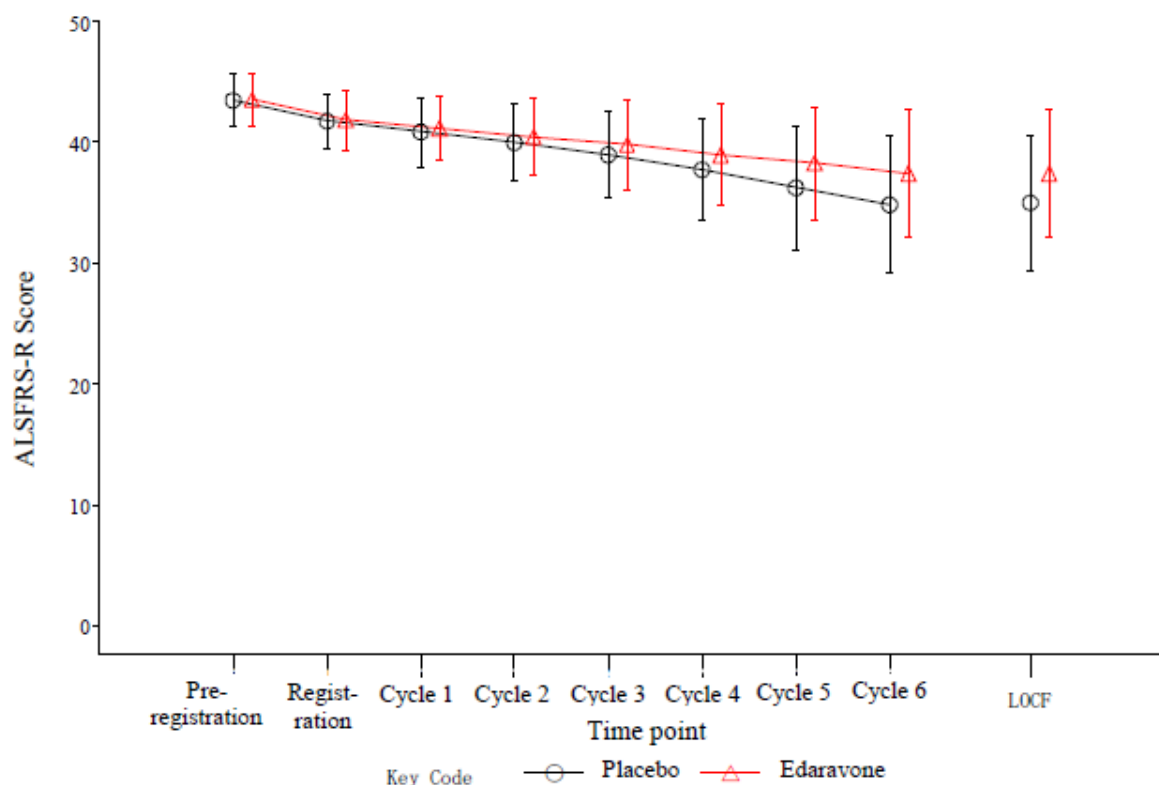
Overall, the two treatment groups were reasonably balanced with regard to baseline demographic and disease data, but there were numerical imbalances for gender (edaravone 55.1% male vs placebo 60.3% male) and ALS disease severity (edaravone 31.9% Grade 1, 68.1% Grade 2 vs placebo 23.5% Grade 1, 76.5% Grade 2). The majority of subjects (~91%) were taking riluzole.

The primary efficacy endpoint was the change in ALSFRS-R from the pre-treatment baseline in Cycle 1 to the end of Cycle 6 (or discontinuation). The primary efficacy analysis was based on an analysis of variance. The two treatment groups were compared using the same factors that were used in dynamic allocation as covariates. For patients with missing values at the end of Cycle 6, data imputation was conducted using the last observation carried forward (LOCF) method.

The change (mean \pm SD) from "baseline in Cycle 1" to "the end of Cycle 6 (or discontinuation, LOCF)" was -4.4 ± 3.8 in the edaravone group and -6.8 ± 4.9 in the placebo group (Figure 6). When assessed by analysis of variance (ANOVA) with the same 3 covariates that were used as factors in dynamic allocation (change in ALSFRS-R score during pre-observation period, El Escorial revised Airlie House diagnostic criteria, and age), the adjusted least square mean (LSMean) \pm standard error (SE) for each treatment group was -5.01 ± 0.64 for the edaravone group and -7.50 ± 0.66 for the placebo group. The between-group difference was 2.49 (95% CI 0.99 to 3.98, $p=0.0013$, Table 19), approximately one third of the placebo rate of change. Multiple pre-specified sensitivity analyses were supportive of the primary analysis.

Table 19 Change in ALSFRS-R score from baseline in Cycle 1 to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% CI)	t-value	P-value
Placebo	-7.50 ± 0.66	2.49 \pm 0.76 (0.99, 3.98)	t=3.29	P=0.0013
Edaravone	-5.01 ± 0.64			

Figure 7 ALSFRS-R score (mean \pm SD) by Time and Treatment Group (FAS), Study 19

Secondary efficacy endpoints were: time to death or certain disease progression (disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech), ALSFRS-R score by domain, %FVC, Modified Norris Scale scores, ALSAQ40 scores, grip strength, pinch grip strength, and Japan ALS severity classification. There was no allowance for multiplicity of secondary endpoints, so the findings should be viewed as nominal.

Time to Death or Certain Disease Progression

There were no deaths during the double-blind phase of the study, so the only events that contributed to this endpoint related to time to disease progression. The number of events was low (6 events in the placebo group and 2 events in the edaravone group, Table 20). The difference between groups was not statistically significant (Table 21).

Table 20 Number of Progression Events (FAS), Study 19

Event	Placebo	Edaravone	Total
Death	0	0	0
Disability of independent ambulation	2	0	2
Loss of upper limbs function	0	0	0
Tracheotomy	0	1	1
Use of respirator	0	0	0
Use of tube feeding	1	0	1
Loss of useful speech	3	1	4

Table 21 Survival analysis for death or certain disease progression (FAS), Study 19

Treatment group	No. of patients	No. of events*	Between-group comparison
Placebo	68	6	$P=0.1284$ (Log-rank test) $P=0.1415$ (Generalized Wilcoxon test)
Edaravone	69	2	

*Death, disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech

For patients with multiple events, the day of onset of the first event was considered the event onset day.

Population analyzed: FAS in the double-blind period. Events that occurred during Cycle 1 to Cycle 6 were analyzed.

ALSFRS-R by Domain

Analyses of change in ALSFRS-R score by domain (bulbar function, limb function, and respiratory function) are shown in Table 22, Table 23, and Table 24. There was no allowance for multiplicity, so these results should be viewed as nominal.

Table 22 Analysis of change in ALSFRS-R score (bulbar function) from baseline in Cycle 1 to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% CI)	t-value	P-value
Placebo	-1.93 \pm 0.25	0.58 \pm 0.29 (0.01, 1.15)	t=2.03	P=0.0448
Edaravone	-1.35 \pm 0.24			

Table 23 Analysis of change in ALSFRS-R score (limb function) from baseline in Cycle 1 to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% CI)	t-value	P-Value
Placebo	-5.12 \pm 0.53	1.61 \pm 0.61 (0.42, 2.81)	t=2.66	P=0.0087
Edaravone	-3.50 \pm 0.51			

Table 24 Analysis of change in ALSFRS-R score (respiratory function) from baseline in Cycle 1 to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% CI)	t-value	P-Value
Placebo	-0.45 \pm 0.13	0.29 \pm 0.15 (-0.01, 0.60)	t=1.90	P=0.0593
Edaravone	-0.16 \pm 0.13			

%FVC

The mean %FVC was close to 100% in each treatment group at baseline, and then declined over the course of the study. There was a trend to greater decline in the placebo group, but the between-group difference did not achieve nominal significance (Table 25).

Table 25 Analysis of change in %FVC from baseline in Cycle 1 to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean ± SE	LSMean ± SE (95% CI)	t-value	P-Value
Placebo	-20.40±2.48	4.78±2.84 (-0.83, 10.40)	t=1.69	P=0.0942
Edaravone	-15.61±2.41			

Modified Norris Scale Score

This was examined with the Limb Norris Scale score, Bulbar Norris Scale score, and the total score (sum of the limb and bulbar scores). Only the total score showed a nominally significant difference between treatment groups by ANOVA (Table 26). The ANOVA analyses for limb (Table 27) and bulbar (Table 28) scores showed weakly favourable trends.

Table 26 Analysis of change in Modified Norris Scale Score (total) from baseline in Cycle 1 to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean ± SE	LSMean ± SE (95% CI)	t-value	P-Value
Placebo	-20.80±2.06	4.89±2.35 (0.24, 9.54)	t=2.08	P=0.0393
Edaravone	-15.91±1.97			

Table 27 Analysis of change in Limb Norris Scale Score from baseline in Cycle 1 to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean ± SE	LSMean ± SE (95% CI)	t-value	P-Value
Placebo	-14.91±1.68	3.44±1.92 (-0.36, 7.24)	t=1.79	P=0.0757
Edaravone	-11.47±1.61			

Table 28 Analysis of change in Bulbar Norris Scale Score from baseline in Cycle 1 to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean ± SE	LSMean ± SE (95% CI)	t-value	P-Value
Placebo	-5.89±0.79	1.46±0.90 (-0.33, 3.24)	t=1.61	P=0.1092
Edaravone	-4.44±0.76			

ALS Quality of Life Assessment (ALSAQ40)

The ALSAQ40 showed a nominally significant improvement in quality of life (increasing score represents worsening QoL) when analysed by ANOVA (p=0.0309, Table 29) and by two-sample t-test (p=0.0295 after Cycle 6 or discontinuation, p=0.0401 after Cycle 6 without LOCF data). It was unclear which items on the ALSAQ40 contributed to this finding, and whether this result is due to the same difference in motor function that was assessed with the ALSFRS-R.

Table 29 Analysis of change in ALSAQ40 score from baseline to the end of Cycle 6 (LOCF), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% CI)	t-value	P-Value
Placebo	26.04 \pm 3.53	-8.79 \pm 4.03 (-16.76, -0.82)	t=-2.18	P=0.0309
Edaravone	17.25 \pm 3.39			

Grip Strength and Pinch-Grip Strength

Analyses of grip strength and pinch-grip strength, measured in kg and averaged across the left and right limb, showed no benefit for these parameters (Table 30, Table 31).

Table 30 Analysis of change in grip strength (mean of the right and left hands) from baseline to the end of Cycle 6 (LOCF) (kg), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% CI)	t-value	P-Value
Placebo	-4.19 \pm 0.56	0.11 \pm 0.64 (-1.15, 1.38)	t=0.18	P=0.8583
Edaravone	-4.08 \pm 0.54			

Table 31 Analysis of change in pinch- grip strength (mean of the right and left hands) from baseline to the end of Cycle 6 (LOCF) (kg), FAS, Study 19

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% CI)	t-value	P-Value
Placebo	-0.88 \pm 0.14	0.10 \pm 0.16 (-0.23, 0.42)	t=0.60	P=0.5478
Edaravone	-0.78 \pm 0.14			

Japan ALS Severity classification

Japan ALS severity classification was presented in a shift table (Table 32) showing a count of subjects according to severity grade at *baseline in Cycle 1* and at *the end of Cycle 6 (or discontinuation)*. No statistical analysis was performed.

Table 32 Shifts in the Japan ALS Severity classification (FAS), Study 19

Treatment group	At baseline in Cycle 1	At the end of Cycle 6 (or at discontinuation)						
		1	2	3	4	5	Missing data	Total
Placebo	1	5	6	3	1	1	0	16
	2	0	17	24	7	0	4	52
	Total	5	23	27	8	1	4	68
Edaravone	1	8	11	3	0	0	0	22
	2	0	17	18	11	0	1	47
	Total	8	28	21	11	0	1	69

Population analyzed: FAS in the double-blind period

Subgroup analyses of the primary endpoint were performed based on the following factors: Sex, Age, Disease duration (<1 year or \geq 1 year), Initial symptom (bulbar vs limb symptoms), El Escorial revised Airlie House diagnostic criteria, Japan ALS severity classification, concomitant

riluzole, complications (presence of ALS complications at baseline), and change in ALSFRS-R score during the pre-observation period (Table 33). Nominal significance was shown across subgroups defined by sex, age, disease duration, and disease severity. These subgroup findings partially offset the concerns with the numerical imbalance in gender and disease severity at baseline.

Table 33 Stratified analysis of ALSFRS-R score (FAS), Study 19

Variable	Category	Time point	Treatment group	Summary statistics				Summary statistics for change from baseline in Cycle 1							Two-sample t-test			
				No. of patients	Mean	SD	Minimum	Maximum	No. of patients	Mean	SD	Minimum	Median	Maximum		Paired t-test		
Sex	Male	At baseline in Cycle 1	Placebo	41	41.6	2.5	37	42.0	47									
		Edaravone	38	41.9	2.9	36	42.5	47										
	At the end of Cycle 6 (or at discontinuation)*	Placebo	39	34.9	6.0	19	35.0	45									P=0.0248	
	Edaravone	38	37.5	5.7	25	38.0	47										P<.0001	
Female	At baseline in Cycle 1	Placebo	27	42.0	1.8	38	42.0	45										
		Edaravone	31	41.8	1.9	38	42.0	45										
	At the end of Cycle 6 (or at discontinuation)*	Placebo	27	35.1	5.1	25	35.0	45									P=0.0278	
	Edaravone	30	37.4	4.8	24	39.5	43										P<.0001	
Age	<65 years	At baseline in Cycle 1	Placebo	46	41.9	2.3	37	42.0	47									
		Edaravone	46	42.2	2.6	36	43.0	47										
	At the end of Cycle 6 (or at discontinuation)*	Placebo	44	35.2	6.1	19	36.0	45										P=0.0211
	Edaravone	46	37.7	5.6	25	39.5	47											P<.0001
Disease duration	≥65 years	At baseline in Cycle 1	Placebo	22	41.5	2.0	38	41.5	45									
		Edaravone	23	41.2	1.9	38	41.0	45										
	At the end of Cycle 6 (or at discontinuation)*	Placebo	22	34.6	4.4	27	35.0	41										P=0.0219
	Edaravone	22	36.9	4.6	24	37.5	43											P<.0001
<1 year	At baseline in Cycle 1	Placebo	33	42.1	2.1	38	42.0	45										
		Edaravone	27	42.8	2.4	38	43.0	47										
	At the end of Cycle 6 (or at discontinuation)*	Placebo	32	35.0	6.1	19	36.5	45										P=0.0317
	Edaravone	27	38.2	4.9	27	39.0	46											P<.0001
≥1 year	At baseline in Cycle 1	Placebo	35	41.5	2.4	37	42.0	47										
		Edaravone	42	41.3	2.3	36	42.0	46										
	At the end of Cycle 6 (or at discontinuation)*	Placebo	34	35.1	5.2	21	35.0	45										P=0.0288
	Edaravone	41	37.0	5.5	24	38.0	47											P<.0001

Variable	Category	Time point	Treatment group	Summary statistics						Summary statistics for change from baseline in Cycle 1						Two-sample t-test			
				No. of patients	Mean	SD	Minimum	Median	Maximum	No. of patients	Mean	SD	Minimum	Median	Maximum		Paired t-test		
Initial symptom	Bulbar symptom	At baseline in Cycle 1	Placebo	14	42.6	1.9	40	42.5	46										
			Edaravone	16	41.6	2.2	38	42.0	46										
	Limb symptom	At the end of Cycle 6 (or at discontinuation)*	Placebo	14	35.6	4.1	29	35.0	42										
			Edaravone	15	37.0	5.4	27	38.0	45										
		At baseline in Cycle 1	Placebo	54	41.6	2.3	37	42.0	47										
			Edaravone	53	42.0	2.5	36	42.0	47										
		At the end of Cycle 6 (or at discontinuation)*	Placebo	52	34.9	6.0	19	35.5	45										
			Edaravone	53	37.6	5.3	24	39.0	47										
	El Escorial revised Arlie House diagnostic criteria	Definite ALS	At baseline in Cycle 1	Placebo	27	41.6	2.2	37	42.0	45									
				Edaravone	28	41.6	2.4	37	42.0	46									
At the end of Cycle 6 (or at discontinuation)*		Placebo	26	35.1	4.4	26	35.0	44											
		Edaravone	28	36.8	6.3	24	40.0	45											
At baseline in Cycle 1		Placebo	41	41.9	2.3	37	42.0	47											
		Edaravone	41	42.1	2.5	36	42.0	47											
At the end of Cycle 6 (or at discontinuation)*		Placebo	40	35.0	6.3	19	36.5	45											
		Edaravone	40	37.9	4.4	28	38.0	47											
Grade 1		At baseline in Cycle 1	Placebo	16	43.3	2.7	37	43.5	47										
			Edaravone	22	43.5	1.7	41	43.0	47										
Japan ALS severity classification	At the end of Cycle 6 (or at discontinuation)*	Placebo	16	38.1	5.1	29	39.0	45											
		Edaravone	22	41.0	2.9	37	41.0	47											
	At baseline in Cycle 1	Placebo	52	41.3	1.9	37	41.5	45											
		Edaravone	47	41.1	2.4	36	41.0	45											
	At the end of Cycle 6 (or at discontinuation)*	Placebo	50	34.0	5.4	19	35.0	44											
		Edaravone	46	35.7	5.3	24	36.0	45											

Variable	Category	Time point	Treatment group	Summary statistics						Summary statistics for change from baseline in Cycle 1						Two-sample t-test				
				No. of patients	Mean	SD	Minimum	Median	Maximum	No. of patients	Mean	SD	Minimum	Median	Maximum		Paired t-test			
Concomitant rihzole	Absent	At baseline in Cycle 1	Placebo	6	40.3	1.6	38	40.5	42	6	-6.4	2.7	-11	-6.0	-4	P=0.0061	P=0.1081			
		Edaravone	6	42.0	3.2	36	43.0	45	6	-3.3	2.9	-8	-3.0	0	P=0.0392					
	Present	At the end of Cycle 6 (or at discontinuation)*	Placebo	5	34.4	3.4	29	35.0	38	61	-6.9	5.0	-20	-5.0	0	P<0.0001	P=0.0042			
		Edaravone	6	38.7	4.3	31	41.0	42	62	-4.5	3.9	-16	-4.0	1	P<0.0001					
		At baseline in Cycle 1	Placebo	62	41.9	2.2	37	42.0	47	61	-6.9	5.0	-20	-5.0	0	P<0.0001				
		Edaravone	63	41.9	2.4	37	42.0	47	62	-4.5	3.9	-16	-4.0	1	P<0.0001					
Complications	Absent	At the end of Cycle 6 (or at discontinuation)*	Placebo	6	38.5	2.3	35	39.0	41	6	-3.8	1.5	-6	-3.5	-2	P=0.0014	P=0.2260			
		Edaravone	4	38.8	3.8	35	38.0	44	4	-2.5	1.7	-4	-3.0	0	P=0.0632					
	Present	At baseline in Cycle 1	Placebo	62	41.7	2.3	37	42.0	47	6	-7.2	5.0	-20	-6.0	0	P<0.0001	P=0.0014			
		Edaravone	65	41.9	2.5	36	42.0	47	64	-4.5	3.9	-16	-4.0	1	P<0.0001					
		At the end of Cycle 6 (or at discontinuation)*	Placebo	60	34.7	5.7	19	35.0	45	60	-7.2	5.0	-20	-6.0	0	P<0.0001				
		Edaravone	64	37.4	5.4	24	39.0	47	64	-4.5	3.9	-16	-4.0	1	P<0.0001					
		At baseline in Cycle 1	Placebo	11	41.0	2.2	37	41.0	44	10	-8.0	4.9	-16	-6.5	-3	P=0.0006		P=0.4016		
		Edaravone	12	40.5	2.0	38	40.0	45	12	-6.3	4.3	-13	-5.5	0	P=0.0003					
		Change in ALSFRS-R score during the pre-observation period	-4, -3	At the end of Cycle 6 (or at discontinuation)*	Placebo	10	33.2	4.4	26	34.0	39	10	-8.0	4.9	-16	-6.5		-3	P=0.0006	P=0.4016
				Edaravone	12	34.2	5.6	27	34.0	42	12	-6.3	4.3	-13	-5.5	0		P=0.0003		
			-2, -1	At baseline in Cycle 1	Placebo	57	41.9	2.2	37	42.0	47	56	-6.6	4.9	-20	-5.0		0	P<0.0001	P=0.0016
				Edaravone	57	42.2	2.4	36	43.0	47	56	-6.6	4.9	-20	-5.0	0		P<0.0001		
At the end of Cycle 6 (or at discontinuation)*	Placebo			56	35.4	5.8	19	36.0	45	56	-6.6	4.9	-20	-5.0	0	P<0.0001				
Edaravone	56			38.2	5.0	24	40.0	47	56	-4.0	3.6	-16	-3.5	1	P<0.0001					

*LOCF used for patients who completed Cycle 3 (patients who reached 81 days after the start of treatment)
 Population analyzed: FAS in the double-blind period

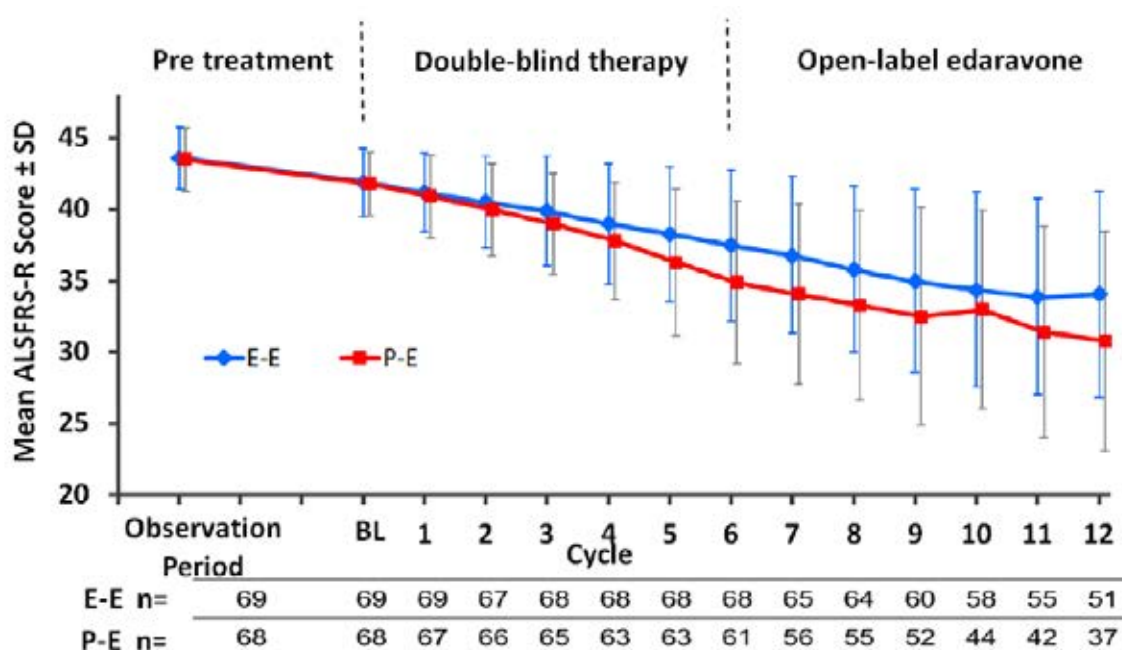
The *active treatment period* of Study 19 involved open-label treatment with edaravone. All subjects who completed Cycle 6 (the double-blind period) in Study 19 were offered the opportunity to receive open-label edaravone for an additional 6 cycles (24 weeks) up to Cycle 12. Study treatment in the Active treatment period was edaravone 60 mg/day administered by IV infusion on 10 of the first 14 days of each 4-week cycle.

58 subjects from the placebo group and 65 subjects from the edaravone group entered the active treatment period, of whom 56 and 65 subjects, respectively, were evaluable for efficacy after Cycle 7, and 37 and 51 subjects, respectively, were evaluable for efficacy after Cycle 12. Discontinuations during the *active treatment period* were higher in the placebo-edaravone (P-E) group than the edaravone-edaravone (E-E) group (18 and 12, respectively).

Efficacy in the active treatment period was assessed using the same efficacy variables as applied in the double-blind period, but all efficacy endpoints were exploratory as the study design prevented any formal hypothesis testing. Interpretation of efficacy in the active treatment period is limited due to the lack of placebo control and the potential for bias (e.g. selection bias, withdrawal bias).

The findings for ALSFRS-R over 12 treatment cycles are shown in Figure 8. The difference between treatment groups at the end of the double-blind phase was largely maintained through to the end of Cycle 12. The study was not designed to provide a formal statistical assessment of the effects of switching to active therapy. The impact of the difference in discontinuations between the groups during the active treatment period remains uncertain.

Figure 9 Change in ALSFRS-R Score (Mean±SD) by Visit up to Cycle 12 (Study 19, FAS, Observed Cases)



The number of events for *death* and *tracheostomy/permanent assisted ventilation* during the double-blind period, the active treatment period, and both periods combined are shown in Table 34.

Table 34 Number of events for “Death” and “Tracheostomy/permanent assisted ventilation or death” for the double-blind period and open-label extension period of Study 19 (MCI186-19 FAS)

Period	Events	Death		Tracheostomy/permanent assisted ventilation or death	
		Group	P-E	E-E	P-E
Double blind period (baseline to end of Cycle 6)	No. of patients	n=68	n=69	n=68	n=69
	No. of events (%)	0 (0.0)	0 (0.0)	2 (2.9)	1(1.4)
Extension period (baseline in Cycle 7 to end of Cycle 12)	No. of patients	n=58	n=65	n=58	n=65
	No. of events (%)	4 (6.9)	2 (3.1)	4 (6.9)	2 (3.1)
Baseline to the end of Cycle 12	No. of patients	n=68	n=69	n=68	n=69
	No. of events (%)	4 (5.9)	2 (2.9)	6 (8.8)	3 (4.3)

Note: For “Death” event, when the outcome of AE was “death” for the patients, the events was also included with efficacy event. “Tracheotomy became necessary” and “Day-long respiratory support apparatus became necessary” in discontinuation reason were also included as “Tracheostomy” and “Permanent assisted ventilation” with efficacy event. The First event date in these multiple events for the patient was analyzed.

Study MCI186-17 (Study 17)

Study 17 was presented as a separate clinical study report, but it was an extension study of Study 16. The study objectives were “to investigate the sustainability of effects of edaravone as well as its long-term efficacy and safety by administering edaravone 60 mg or matching placebo once daily in a double-blind, parallel-group comparison in patients who have completed Study 16 In addition, to collect information when edaravone administration is resumed following placebo administration.” It was conducted in multiple centres in Japan between 8 May 2006 and 12 May 2009.

All subjects who completed Study 16 without meeting discontinuation criteria were eligible to enter Study 17. Study 17 used a double-blind, placebo-controlled design in which placebo recipients from Study 16 were allocated to edaravone, and edaravone recipients from Study 16 were randomised on a 1:1 basis to continue edaravone or change to placebo (Table 35). The randomisation was done at the time of the original randomisation for Study 16. Following six cycles of treatment in the extension study (Cycles 7-12), all subjects were allocated to receive open-label edaravone for a further three cycles (Cycles 13-15).

Study treatment from Cycle 7 to Cycle 12 was edaravone 60 mg or matching placebo administered by IV infusion on 10 days in the first 14 days of each 4-week cycle. Study treatment from Cycle 13 to Cycle 15 for all subjects was open-label edaravone 60 mg administered by IV infusion on 10 days in the first 14 days of each 4-week cycle. The treatment groups were named according to treatment allocation in Studies 16 and 17 (Table 36), and are abbreviated in this report as EE, EP, and PE.

Table 35 Overview of the Confirmatory Study (Study 16) and the Extension Study (Study 17)

Confirmatory study			Extension study	
Pre-observation period (3 months)	(6 months)		(6 months)	(3 months)
(No treatment)	Assignment	Edaravone group	Edaravone group	Edaravone group
		Placebo group	Placebo group	
		Placebo group	Edaravone group	

Table 36 Treatment group names

Group	Confirmatory study (Cycles 1 to 6)	Extension study (Cycles 7 to 12)	Extension study (Cycles 13 to 15)
Edaravone-edaravone group	Edaravone group	Edaravone group	Edaravone group
Edaravone-placebo group	Edaravone group	Placebo group	Edaravone group
Placebo-edaravone group	Placebo group	Edaravone group	Edaravone group

The efficacy endpoint was ALSFRS-R. Other efficacy endpoints were time to death or certain disease progression (disability of independent ambulation, loss of upper limbs function, tracheostomy, use of respirator, and use of tube feeding), ALSFRS-R score by domain, %FVC, Modified Norris Scale scores, ALSAQ40 scores, grip strength, pinch grip strength, and Japan ALS severity classification.

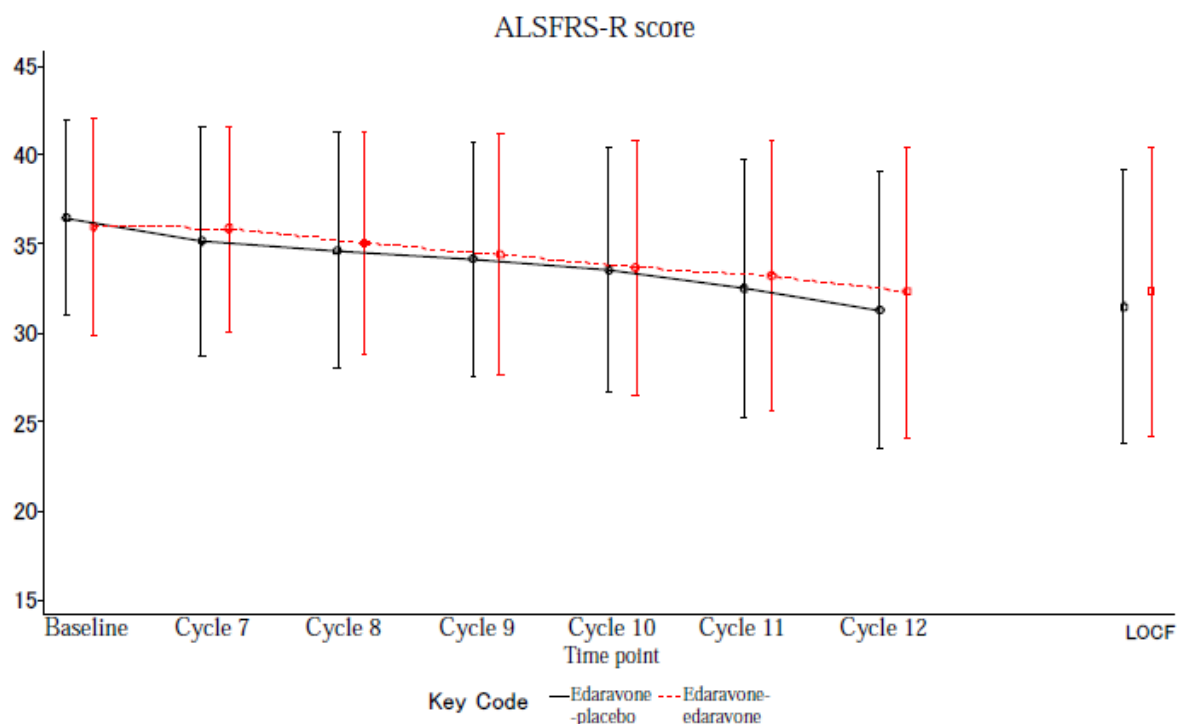
The analysis populations and statistical methods were similar to Study 16. The primary analysis focussed on changes between baseline in Cycle 7 and end of Cycle 12 or discontinuation. The primary comparison was between the EE and EP groups, with results in the PE group largely presented with descriptive statistics. No correction was applied to account for multiplicity of analysis methods and secondary endpoints.

181 patients were enrolled in Study 17 (45 in the EP group, 48 in the EE group, and 88 in the PE group). The FAS comprised 180 patients (44 in the EP group, 48 in the EE group, and 88 in the PE group).

Study 17 was negative for its primary endpoint, showing no significant benefit in change in ALSFRS-R from baseline in Cycle 7 to end of Cycle 12 or discontinuation (Table 37). The EP and EE groups showed similar declines in ALSFRS-R over the 6 cycles (Figure 9).

Table 37 Analysis of change in ALSFRS-R from baseline in Cycle 7 to end of Cycle 12 (LOCF), FAS, Study 17

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% confidence interval)	<i>t</i> -value	<i>P</i> -value
Edaravone-placebo	-5.58 \pm 0.74	1.16 \pm 0.93 (-0.70, 3.01)	<i>t</i> =1.24	<i>P</i> =0.2176
Edaravone-edaravone	-4.42 \pm 0.69			

Figure 102 ALSFRS-R score (mean \pm SD) (FAS), Study 17

As in Study 16, the Sponsor performed an analysis in the *EESP* sub-population, defined as the FAS after exclusion of patients with the following:

- score of ≤ 1 point on any item in the ALSFRS-R at baseline in Cycle 1.
- %FVC <80% at baseline in Cycle 1.

The decision to use the *EESP* population as an additional dataset for Study 17 was made after the results of Study 16 were available, but before final breaking of the code for Study 17. The *EESP* comprised 96 patients (25 in the EP group, 27 in the EE group, and 44 in the PE group). The between-group difference for the primary efficacy variable in the *post hoc* analysis of the *EESP* sub-population was slightly more favourable than the FAS (LSMean 1.85 vs 1.16, respectively) but the *EESP* result still did not achieve nominal significance, even without correction for multiplicity (Table 38).

Table 38 Change in ALSFRS-R score from Baseline, Cycle 7 to End of Cycle 12 (LOCF), *EESP*, Study 17

Treatment group	Adjusted mean	Between-group difference in adjusted mean		
	LSMean \pm SE	LSMean \pm SE (95% confidence interval)	<i>t</i> -value	<i>P</i> -value
Edaravone-placebo	-5.86 \pm 0.98	1.85 \pm 1.14 (-0.45, 4.15)	<i>t</i> =1.62	<i>P</i> =0.1127
Edaravone-edaravone	-4.01 \pm 0.86			

Other efficacy endpoints were generally negative, showing no significant difference between the EP and EE groups. The only nominally significant finding was for the limb component of the Modified Norris Scale, but no adjustment was applied for multiplicity. Change in %FVC was less favourable in the EE group than the EP group (LSMean -13.33 vs -10.15, respectively).

Findings for death or certain disease progression did not support a benefit from switching to, or remaining on, edaravone (Table 39). Of the two smaller groups, overall events were numerically higher in the EE group than the EP group, including 4 of the 6 deaths overall. The PE group, which comprised nearly half of the total patients, accounted for approximately half of the total events.

Table 39 Number of events defined as death or certain disease progression (all cycles) (FAS), Study 17

Event name*	Edaravone-placebo	Edaravone-edaravone	Placebo-edaravone	Total
Death	1	4	1	6
Disability of independent ambulation	12	13	29	54
Loss of upper limbs function	5	6	11	22
Tracheotomy	0	6	6	12
Use of respirator	0	4	5	9
Use of tube feeding	4	4	10	18

*: Events that occurred by the end of Cycle 15

Study MCI-186-18 (Study 18)

This was a multi-centre, double-blind, parallel-group, placebo-controlled, exploratory study to explore the efficacy and safety of edaravone in patients with Grade 3 ALS (Japan ALS severity classification). The study was conducted in Japan between 21 December 2006 and 29 July 2008.

The study included a 12-week observation period followed by a 24-week double-blind treatment period (six cycles of treatment). Study treatment was edaravone 60 mg (or matching placebo) administered by IV infusion on the first 14 days of Cycle 1 (followed by no treatment for 14 days), and then on 10 of the first 14 days of each subsequent 28-day treatment cycle.

The inclusion criteria were:

- Patients who correspond to “definite ALS”, “probable ALS”, or “probable-laboratory-supported ALS” by the El Escorial revised Airlie House diagnostic criteria
- Patients with severity grade 3 ALS by the Japan ALS severity classification
- Patients whose % forced vital capacity (%FVC) is 60% or higher
- Patients who are within 3 years after the onset of ALS at written informed consent
- Patients between 20 and 75 years old at written informed consent
- Patients who gave written informed consent to study participation
- Patients whose ALSFRS-R score changed by -1 to -4 points during the 12-week pre-observation period.

The study was exploratory, and it was not adequately powered. The planned sample size was 10 patients per group, and this appeared to be based on logistical convenience.

25 patients were randomised 1:1 to treatment (13 to edaravone and 12 to placebo), with dynamic allocation based on ALSFRS-R score changes during the 12-week pre-observation period (-1, -2 vs -3, -4). Baseline demographic and disease characteristics were reasonably balanced for a small exploratory study.

The analysis populations and statistical methods were similar to the other Phase 3 studies. No correction was applied to compensate for the multiplicity of analysis methods and secondary endpoints.

The efficacy variable was the ALSFRS-R score, and other endpoints were time to death or certain disease progression, domain-specific ALSFRS-R score, %FVC, Modified Norris Scale score, ALSAQ40 score, grip strength, pinch-grip strength, and Japan ALS severity classification.

This study was negative for its defined endpoints, with no significant difference between the edaravone and placebo groups. ALSFRS-R scores over the duration of the study are shown in

Figure 10. In the analysis of change in ALSFRS-R score from baseline in Cycle 1 to the end of Cycle 6 or discontinuation (LOCF), there was a numerically greater decrease in the edaravone group than placebo (Table 40). Other analyses of ALSFRS-R scores failed to show any benefit of edaravone over placebo. Similarly, analyses of secondary endpoints failed to show any benefit of edaravone over placebo. Events of death or certain disease progression were numerically greater with edaravone than placebo (Table 41).

Figure 31 ALSFRS-R score (mean \pm S.D.) (FAS), Study 18

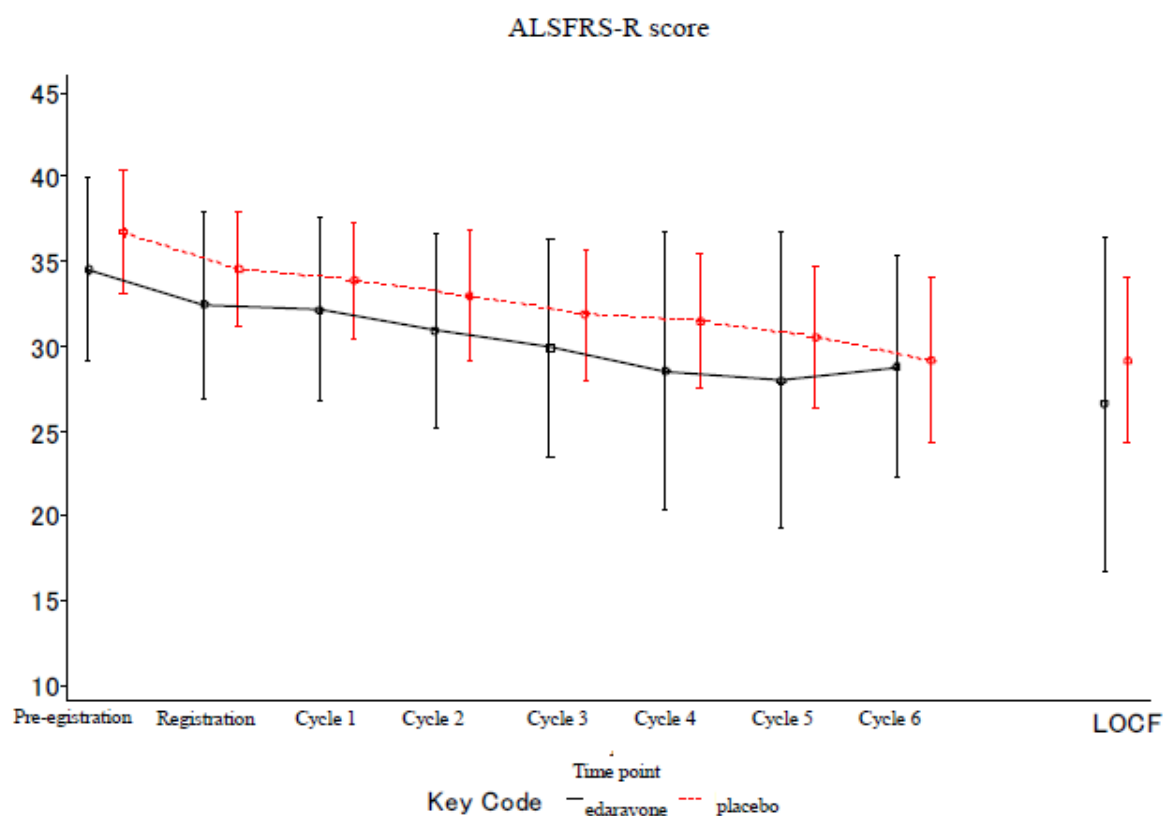


Table 40 Analysis of changes in ALSFRS-R score from baseline in Cycle 1 to the end of Cycle 6 (LOCF) (FAS), Study 18

Group	Adjusted mean	Between-group differences in the adjusted mean		
	LS Mean \pm S.E.	LS Mean \pm S.E. (95% C.I.)	<i>t</i> -value	<i>P</i> -value
Placebo	-6.00 \pm 1.83	-0.52 \pm 2.46 (-5.62, 4.58)	<i>t</i> = -0.21	<i>P</i> = 0.8347
Edaravone	-6.52 \pm 1.78			

Table 41 Death or certain disease progression; number of events (FAS), Study 18

Event	Placebo	Edaravone	Total
Death	0	1	1
Disability of independent ambulation	2	4	6
Loss of upper arm function	2	1	3
Tracheotomy	0	0	0
Use of respirator	0	0	0
Use of tube feeding	0	1	1

Safety

The clinical safety dataset included safety data from:

- 5 Phase 2 or 3 studies in patients with ALS (Table 42).
- 5 Phase 1 PK studies in healthy volunteers.
- 4 post-marketing PK and PD studies, 2 evaluating effects of hepatic impairment, 1 evaluating effects of renal impairment, and 1 evaluating effects on QT.
- 8 studies in patients with AIS, and 3 studies in patients with SAH.

Table 42 Clinical Studies in patients with ALS

Study No.	Study Category	Study Description	Study Design	Population	Number of Subjects (Safety Analysis Set)	Dosage and Administration	Dosage Period
MCI186-12	Phase II	A Phase II, exploratory study of edaravone in subjects with ALS	Open-label uncontrolled	ALS patients	19 subjects (30 mg group: 5 subjects, 60 mg group: 14 subjects)	Edaravone 30 mg or 60 mg Once a day IV infusion	Cycle 1: Administration for 14 consecutive days, followed by a drug-free period of 2 weeks Cycle 2 to 6: Administration of 5 days per week x 2 weeks, followed by a drug-free period of 2 weeks
MCI186-16	Phase III	A Phase III, double-blind, parallel-group study of edaravone for treatment of ALS (confirmatory study)	Randomized, double-blind, placebo-controlled, parallel group, comparative	ALS patients (Grade 1 or 2 ^b)	206 subjects (P group: 104 subjects, E group: 102 subjects)	Edaravone 60 mg or placebo. Once a day IV infusion	Cycle 1: Administration for 14 consecutive days, followed by a drug free period of 2 weeks Cycle 2 to 6: Administration for a total of 10 days over 2 weeks, followed by a drug-free period of 2 weeks
MCI186-17	Phase III	A Phase III, double-blind, parallel-group study of edaravone for treatment of ALS (extension study of MCI186-16)	Double-blind, placebo-controlled, parallel group, comparative	ALS patients	181 subjects (EP group: 45 subjects, EE group: 48 subjects, PE group: 88 subjects)	Edaravone 60 mg or placebo. Once a day IV infusion	Cycle 7 to 15 (continued from MCI186-16): Administration for a total of 10 days over 2 weeks, followed by a drug-free period of 2 weeks Cycle 13 to 15: Active treatment
MCI186-18	Phase III	A Phase III, double-blind, parallel-group study of edaravone for treatment of ALS severity Grade 3 (exploratory study)	Randomized, double-blind, placebo-controlled, parallel group, comparative, exploratory	ALS patients (Grade 3 ^d)	25 subjects (P group: 12 subjects, E group: 13 subjects)	Edaravone 60 mg or placebo. Once a day IV infusion	Cycle 1: Administration for 14 consecutive days, followed by a drug free period of 2 weeks Cycle 2 to 6: Administration for a total of 10 days per 2 weeks, followed by a drug-free period of 2 weeks
MCI186-19	Phase III	A Phase III, double-blind, parallel-group study of edaravone for treatment of ALS (second confirmatory study)	Randomized, double-blind, placebo-controlled, parallel group, comparative, with 6-month active treatment period	ALS (Grade 1 or 2 ^d)	137 subjects ^b (P group: 68 subjects, E group: 69 subjects) ^c 123 subjects ^c (P-E group: 58 subjects, E-E group: 65 subjects)	Edaravone 60 mg or placebo. Once a day IV infusion	Cycle 1: Administration for 14 consecutive days, followed by a drug free period of 2 weeks Cycle 2 to 12: Administration for a total of 10 days over 2 weeks, followed by a drug-free period of 2 weeks

Exposure to edaravone in patients with ALS was limited. A total of 349 patients received edaravone in the ALS clinical trial program, including 306 subjects who received edaravone for at least 6 months (6 cycles), and 98 subjects who received edaravone for at least 12 months (12 cycles). With the exception of 5 patients in the Phase 2 study who received edaravone 30 mg/day, patients treated with edaravone in the ALS studies received edaravone 60 mg/day on 14 consecutive days followed by 14 days of no treatment in the first cycle, and then on 10 of 14 days, followed by 14 days of no treatment, for each subsequent cycle. Treatment in the AIS studies was for 14 days, mostly at a dose of 30 mg twice a day (BD). Similarly, treatment in the SAH studies was for 14 days, mostly at a dose of 120 mg/day.

The overall incidences of AEs, drug-related AEs, and SAEs in the placebo-controlled ALS dataset (Safety Integrated Analysis Set 1) were similar between the edaravone and placebo groups (Table 43). Treatment emergent adverse events (TEAEs) by System Organ Class (SOC) and Preferred Term (PT) are summarised in Table 44. The most frequently reported TEAEs with edaravone ($\geq 3\%$ and greater than placebo) were contusion (14.7% vs. 8.7%), gait disturbance (12.5% vs. 9.2%), headache (8.2% vs. 5.4%), eczema (6.5% vs. 2.2%), dermatitis contact (6.0% vs. 3.3%), respiratory disorder (4.3% vs. 1.1%), rash (3.8% vs. 2.2%), glucose urine present (3.8% vs. 1.6%), and upper respiratory tract inflammation (3.3% vs. 1.6%). Analyses of TEAEs by severity did not identify specific safety concerns (Table 45).

There were 6 treatment-emergent deaths in the placebo-controlled ALS studies (cycles 1 - 6), 4 in the edaravone group and 2 in the placebo group. In subsequent cycles (7 - 12), the incidence of death was similar across treatment groups. The most common cause of death was respiratory failure, as expected for a population of subjects with ALS. Analyses of serious AEs (SAEs) in the ALS studies did not identify notable safety concerns.

TEAEs leading to discontinuation of study drug were reported in 2.2% of subjects in the edaravone group and 5.4% of subjects in the placebo group. One patient treated with edaravone discontinued due to an AE that was thought to be potentially drug-related (“toxic skin eruption” in Cycle 1, which resolved and was rated as non-serious).

Table 43 Overview of TEAEs [Placebo-Controlled Studies (Cycle 1 through 6) - Safety Integrated Analysis Set 1]

	Placebo N = 184		Edaravone N = 184	
	n (%)	No. of Events	n (%)	No. of Events
AEs	160 (87.0)	501	161 (87.5)	487
AEs leading to discontinuation	10 (5.4)	10	4 (2.2)	4
Drug-related AEs	26 (14.1)	30	19 (10.3)	23
Drug-related AEs leading to discontinuation	3 (1.6)	3	1 (0.5)	1
SAEs	41 (22.3)	60	32 (17.4)	46
Drug-related SAEs	0 (0.0)	0	0 (0.0)	0
Death	2 (1.1)	2	4 (2.2)	4

Drug-related AEs (and SAEs) are based on Investigator assessment.

Table 44 Incidence of TEAEs Occurring in at Least 2% of Subjects in the Pooled Edaravone Group and Greater than Placebo Pooled [Placebo-Controlled Studies (Cycle 1 through 6) - Safety Integrated Analysis Set 1]

SOC PT	Placebo (N=184)		Edaravone (N=184)	
	n	(%)	n	(%)
Any AE ^a	160	(87.0)	161	(87.5)
Infections and infestations ^a	57	(31.0)	63	(34.2)
Tinea pedis	2	(1.1)	4	(2.2)
Upper respiratory tract infection	3	(1.6)	5	(2.7)
Nervous system disorders ^a	23	(12.5)	26	(14.1)
Headache	10	(5.4)	15	(8.2)
Respiratory, thoracic and mediastinal disorders ^a	24	(13.0)	26	(14.1)
Respiratory disorder	2	(1.1)	8	(4.3)
Upper respiratory tract inflammation	3	(1.6)	6	(3.3)
Gastrointestinal disorders ^a	68	(37.0)	57	(31.0)
Nausea	1	(0.5)	4	(2.2)
Skin and subcutaneous tissue disorders ^a	37	(20.1)	47	(25.5)
Dermatitis contact	6	(3.3)	11	(6.0)
Eczema	4	(2.2)	12	(6.5)
Erythema	3	(1.6)	5	(2.7)
Rash	4	(2.2)	7	(3.8)
Musculoskeletal and connective tissue disorders ^a	39	(21.2)	36	(19.6)
Myalgia	2	(1.1)	4	(2.2)
General disorders and administration site conditions ^a	37	(20.1)	41	(22.3)
Gait disturbance	17	(9.2)	23	(12.5)
Investigations ^a	14	(7.6)	13	(7.1)
Glucose urine present	3	(1.6)	7	(3.8)
Injury, poisoning and procedural complications ^a	36	(19.6)	39	(21.2)
Ligament sprain	4	(2.2)	5	(2.7)
Excoriation	3	(1.6)	5	(2.7)
Contusion	16	(8.7)	27	(14.7)

MedDRA version 17.0. A subject reporting more than 1 TEAE for a particular PT or SOC is counted only once for that PT or SOC.

Includes TEAEs with an incidence $\geq 2\%$ in the pooled edaravone group and greater than the pooled placebo group.

^a Count for all subjects who had at least 1 TEAE.

Table 45. Incidence of TEAEs Occurring in at Least 2% of Subjects in the Pooled Edaravone Group by Severity [Placebo-Controlled Studies (Cycle 1 through 6) - Safety Integrated Analysis Set 1]

System Organ Class Preferred Term	Placebo (N=184)			Edaravone (N=184)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Any AE ^a	94 (51.1)	38 (20.7)	28 (15.2)	98 (53.3)	41 (22.3)	22 (12.0)
Infections and infestations ^a	52 (28.3)	5 (2.7)	0 (0.0)	59 (32.1)	4 (2.2)	0 (0.0)
Nasopharyngitis	29 (15.8)	0 (0.0)	0 (0.0)	27 (14.7)	0 (0.0)	0 (0.0)
Pharyngitis	5 (2.7)	0 (0.0)	0 (0.0)	5 (2.7)	0 (0.0)	0 (0.0)
Tinea pedis	2 (1.1)	0 (0.0)	0 (0.0)	4 (2.2)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	3 (1.6)	0 (0.0)	0 (0.0)	5 (2.7)	0 (0.0)	0 (0.0)
Psychiatric disorders ^a	17 (9.2)	2 (1.1)	1 (0.5)	14 (7.6)	0 (0.0)	0 (0.0)
Insomnia	14 (7.6)	1 (0.5)	0 (0.0)	14 (7.6)	0 (0.0)	0 (0.0)
Nervous system disorders ^a	20 (10.9)	0 (0.0)	3 (1.6)	25 (13.6)	1 (0.5)	0 (0.0)
Headache	10 (5.4)	0 (0.0)	0 (0.0)	15 (8.2)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders ^a	11 (6.0)	7 (3.8)	6 (3.3)	14 (7.6)	5 (2.7)	7 (3.8)
Upper respiratory tract inflammation	3 (1.6)	0 (0.0)	0 (0.0)	5 (2.7)	1 (0.5)	0 (0.0)
Gastrointestinal disorders ^a	45 (24.5)	12 (6.5)	11 (6.0)	36 (19.6)	15 (8.2)	6 (3.3)
Constipation	23 (12.5)	0 (0.0)	1 (0.5)	22 (12.0)	1 (0.5)	0 (0.0)
Diarrhoea	9 (4.9)	0 (0.0)	0 (0.0)	8 (4.3)	0 (0.0)	0 (0.0)
Dysphagia	1 (0.5)	11 (6.0)	9 (4.9)	0 (0.0)	12 (6.5)	6 (3.3)
Skin and subcutaneous tissue disorders ^a	36 (19.6)	1 (0.5)	0 (0.0)	46 (25.0)	1 (0.5)	0 (0.0)
Dermatitis contact	6 (3.3)	0 (0.0)	0 (0.0)	11 (6.0)	0 (0.0)	0 (0.0)
Eczema	4 (2.2)	0 (0.0)	0 (0.0)	12 (6.5)	0 (0.0)	0 (0.0)
Erythema	3 (1.6)	0 (0.0)	0 (0.0)	5 (2.7)	0 (0.0)	0 (0.0)
Rash	3 (1.6)	1 (0.5)	0 (0.0)	7 (3.8)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders ^a	21 (11.4)	9 (4.9)	9 (4.9)	24 (13.0)	8 (4.3)	4 (2.2)
Back pain	7 (3.8)	0 (0.0)	0 (0.0)	6 (3.3)	1 (0.5)	0 (0.0)
Musculoskeletal disorder	0 (0.0)	1 (0.5)	5 (2.7)	0 (0.0)	0 (0.0)	4 (2.2)
Muscular weakness	1 (0.5)	6 (3.3)	3 (1.6)	1 (0.5)	6 (3.3)	1 (0.5)
General disorders and administration site conditions ^a	19 (10.3)	13 (7.1)	5 (2.7)	18 (9.8)	10 (5.4)	13 (7.1)
Gait disturbance	2 (1.1)	10 (5.4)	5 (2.7)	3 (1.6)	10 (5.4)	10 (5.4)
Investigations	13 (7.1)	1 (0.5)	0 (0.0)	13 (7.1)	0 (0.0)	0 (0.0)
Glucose urine present	3 (1.6)	0 (0.0)	0 (0.0)	7 (3.8)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications ^a	27 (14.7)	9 (4.9)	0 (0.0)	31 (16.8)	8 (4.3)	0 (0.0)
Ligament sprain	3 (1.6)	1 (0.5)	0 (0.0)	5 (2.7)	0 (0.0)	0 (0.0)
Excoriation	3 (1.6)	0 (0.0)	0 (0.0)	5 (2.7)	0 (0.0)	0 (0.0)
Contusion	16 (8.7)	0 (0.0)	0 (0.0)	25 (13.6)	2 (1.1)	0 (0.0)

MedDRA version 17.0. A subject reporting > 1 TEAE for a particular PT or SOC is counted only once for that PT or SOC. In addition, if TEAEs of differing severities developed in the same subject, the TEAEs were tabulated under the greatest severity.

^a Count for all subjects who had at least 1 TEAE.

AEs by organ system (hepatic, renal, respiratory, skin) in the ALS studies were reviewed. There was no evidence of an increased incidence of hepatic or renal AEs in subjects exposed to edaravone. Respiratory AEs were overall similar across the treatment groups. Skin AEs were more frequent in the edaravone group compared to placebo (23.4% vs. 19.6%, Safety Integrated Analysis Set 1). Most Skin TEAEs were mild, 2 were moderate in severity (both led to discontinuation), and none were severe or serious.

No clinically important safety concerns were identified in the ALS studies with regard to treatment-emergent changes in liver function tests, renal function, and haematological parameters. No subjects met the criteria for Hy's law.

Urinalysis showed a higher incidence of elevated urinary glucose in edaravone recipients than placebo recipients in the placebo-controlled dataset (23.9% vs. 17.4%), and TEAEs for *glucose urine present* were reported more frequently in the edaravone group than placebo (3.8% vs.

1.6%). The clinical significance of these glycosuria findings is uncertain as blood glucose and glycated haemoglobin (HbA1c) were not monitored in the ALS studies. The Sponsor indicated that the lack of monitoring of blood glucose and HbA1c in the ALS studies was based on experience in AIS.

ECGs were not routinely assessed in the ALS studies. The Sponsor reported that *“In the 5 ALS clinical studies (1 Phase 2 study and 4 Phase 3 studies), ECG was not established as an examination parameter. The ECGs were not assessed during treatment or at the end of dosing and any quantitative analyses of results of ECGs are not available.”* An independent cardiological review of ECGs obtained in healthy volunteer studies found no evidence of any issues. A post-marketing QT study (MCI-186-J25) showed no evidence of a significant QT effect from edaravone, even at a suprathreshold dose of 300 mg.

Hypersensitivity reactions, including anaphylaxis and shock, have been identified as clinically significant adverse drug reactions (ADR) associated with edaravone treatment, based on post-marketing experience in AIS patients in Japan. One case of shock was reported in the ALS studies (Study 19). Post-marketing safety reviews have identified additional cases of anaphylactic reaction/shock.

Analyses of safety by age and gender did not identify specific safety concerns.

The non-clinical program identified a potential risk of treatment-related neurotoxicity. There was no clear safety signal for neurotoxicity in the ALS clinical studies; however, this does not exclude the possibility of neurotoxicity as the safety dataset in ALS was relatively small, the double-blind period of the confirmatory studies was only 24 weeks duration, and neurological sequelae arising from drug-related neurotoxicity may be difficult to distinguish in patients with a progressive neurodegenerative condition.

As of 4 November 2017, approximately 4,000 ALS patients and 1.76 million AIS patients have been exposed to edaravone since the first approval in April 2001. The submission presented limited post-marketing data in ALS which did not change the safety profile for ALS. The Sponsor also presented a review of post-marketing safety data for non-ALS indications as of 25 December 2015. A total of 2,451 AEs (2,205 ADRs) had been reported spontaneously among AIS patients in Japan for commercially available edaravone. The most frequently reported ADRs among AIS patients (100 or more cases) were renal and urinary disorders (518 cases), hepatobiliary disorders (474 cases), investigations (313 cases), skin and subcutaneous tissue disorders (130 cases), blood and lymphatic system disorders (125 cases), and general disorders and administration site conditions (120 cases).

Discussion

Efficacy

The submission presented four Phase 3 efficacy studies in patients with ALS:

- Study 16, the initial confirmatory study in patients with Grade 1 or 2 ALS.
- Study 19, the second confirmatory study designed to assess efficacy in a restricted population based on *post hoc* findings from Study 16.
- Study 17, an extension study of Study 16.
- Study 18, an exploratory study in patients with Grade 3 ALS.

Study 19 was the only study to demonstrate a therapeutic benefit, showing a significant reduction in the decline in the primary efficacy variable, ALSFRS-R, over 6 cycles of treatment compared to placebo. Studies 16, 17, and 18 were all negative studies which failed to demonstrate a significant benefit for the primary endpoints. Consequently, Study 19 is the pivotal study for efficacy in this application.

Study 19 evaluated efficacy in a restricted population of patients with Grade 1 or 2 ALS based on the criteria used to define the *definite or probable/EESP/2y* population in the *post hoc* analysis of Study 16:

- “Definite” or “Probable” ALS diagnosis according to El Escorial revised Airlie House diagnostic criteria.
- less than 2 years since symptom onset.
- each item of the ALSFRS-R score ≥ 2 .
- normal respiratory function (%FVC $\geq 80\%$).

Subjects also needed to have a decline in ALSFRS-R score of 1 to 4 points during the 12-week pre-observation period of the study in order to be eligible for the randomised-controlled part of the study.

Study 19 met its primary endpoint, i.e. change in ALSFRS-R from baseline in Cycle 1 to the end of Cycle 6 (or discontinuation). The adjusted LSMean change in ALSFRS-R was -5.01 for the edaravone group and -7.50 for the placebo group, a difference of 2.49 (95% CI: 0.99, 3.98, $p=0.0013$). Multiple sensitivity analyses were supportive of the primary analysis. The magnitude of the demonstrated benefit in ALSFRS-R is likely to be clinically meaningful.

Secondary efficacy endpoints were inconsistent in supporting a treatment benefit. Some, but not all, of the secondary endpoints reached nominal significance, but no adjustment was applied for multiplicity. The overall number of events for *time to death or certain disease progression* was low (6 events in the placebo group, 2 events in the edaravone group) and the difference between groups did not reach nominal significance. There were no deaths during the double-blind treatment period, so the study was not able to demonstrate a survival benefit for edaravone compared to placebo. *Change in ALSFRS-R score by domain* showed inconsistent results, with nominally significant results for the bulbar and limb components, but not for the respiratory component. For %FVC, there was a trend to greater decline in the placebo group, but the between-group difference did not achieve nominal significance. The *Modified Norris Scale Score* showed a nominal benefit for total score, but not for the bulbar or limb scores. The *ALSAQ40* showed a nominally significant improvement in quality of life. No benefit was observed for grip strength or pinch-grip strength.

Interpretation of efficacy findings in the *active treatment period* of Study 19 is limited as all patients in this phase of the study received open-label edaravone.

The initial confirmatory study, Study 16, was a randomised, placebo-controlled study designed to evaluate the efficacy of edaravone in patients with ALS Grade 1 or 2. This study was negative for its primary endpoint, change in ALSFRS-R, and secondary endpoints, including progression milestones, functional assessments, and strength assessments. Consequently, this study does not support the efficacy of edaravone in patients with Grade 1 or 2 ALS. A *post hoc* analysis after data unblinding applied multiple restrictive selection criteria to show nominally significant treatment effects in the *EESP* and *definite or probable/EESP/2y* sub-populations. The *definite or probable/EESP/2y* sub-population excluded ~65% of subjects in the FAS. From this process, the Sponsor generated the hypothesis that efficacy of edaravone may be demonstrable in a restricted population of patients. The *post hoc* findings from Study 16 informed the design of Study 19 but should not be relied on as evidence of efficacy because the restricted population was identified after efficacy outcomes were known.

Study 17, an extension of Study 16, used a randomised, placebo-controlled design to assess the benefit of continuing edaravone versus switching to placebo in subjects who had completed Study 16. It also assessed efficacy in subjects treated with placebo in Study 16 and edaravone in Study 17. No significant benefit was observed with edaravone compared to placebo for the primary endpoint, change in ALSFRS-R score. The majority of secondary endpoints were also negative, with the exception of the limb component of the Modified Norris Scale, which showed a nominally significant difference, but no adjustment was applied for multiplicity. Analysis of the

primary efficacy variable in the *EESP* sub-population showed a numerically favourable trend that did not achieve nominal significance.

Study 18 showed no evidence of efficacy of edaravone in patients with Grade 3 ALS. In fact, the primary endpoint trended in favour of placebo.

Given the negative findings from Studies 16, 17, and 18, the application is reliant on Study 19 to establish efficacy in the proposed indication. The primary outcome from Study 19 was a significant reduction in the decline in ALSFRS-R score (i.e. benefit in functional status) in a restricted sub-population of patients over 6 cycles of treatment. The applicability of the results to a broader population of ALS patients is uncertain, particularly in the context of the negative findings from Study 16. The study did not demonstrate a survival benefit (no patients died during the double-blind period) and secondary efficacy endpoints did not consistently support a treatment benefit. Some, but not all, of the secondary endpoints showed a nominally significant benefit, but no adjustment was applied for multiplicity. A numerical imbalance in ALS disease severity between the groups at baseline, and a higher discontinuation rate in the placebo group, could have impacted the study outcomes.

The lack of a demonstrated benefit on survival is a notable deficiency of the application, as the TGA-adopted *CHMP guideline on clinical investigation of medicinal products for the treatment of ALS* recommends that confirmatory studies for disease modifying treatments should address both functioning and survival. A functional measure, such as ALSFRS-R, is acceptable as a primary endpoint, but should be supported by a survival endpoint as a major endpoint in confirmatory studies. Study 19 evaluated change in ALSFRS-R as the primary endpoint, and *time to death or certain disease progression* as a secondary endpoint. *Time to death or certain disease progression* is not strictly a survival endpoint as it includes a range of markers of disease progression beyond those which may confound survival data. Study 19 failed to demonstrate a survival benefit or a significant benefit in *time to death or certain disease progression*. No deaths occurred in either group in the double-blind phase of the study and the number of certain disease progression events was low. Similarly, Study 16 failed to demonstrate a survival benefit or a benefit in *time to death or certain disease progression*. The CHMP guideline advises that duration of the confirmatory study would depend on the expected rate of progression, and “study duration of 12-18 months may be sufficient”. The double-blind periods of the two confirmatory studies, Study 16 and 19, were 24 weeks duration. It remains uncertain whether the failure to demonstrate a survival benefit was due to lack of efficacy or inadequate study duration.

The findings from Study 19 have not been replicated in another study. In cases where the confirmatory evidence is provided by only one pivotal study, the findings from that study should be particularly compelling.⁵ In this application, there are concerns with regard to internal validity (a numerical imbalance in ALS disease severity between the groups at baseline, and a higher discontinuation rate in the placebo group, could have influenced the study outcomes), external validity (it remains uncertain whether the treatment benefit observed in the restricted population of Study 19 can be generalised to a broader population of patients, particularly in the context of the failure to demonstrate a benefit in a broader population of patients with Grade 1-2 ALS in Study 16), and internal consistency (no survival benefit was demonstrated, and secondary efficacy endpoints were not statistically robust and did not consistently support the primary outcome).

Safety

The safety dataset in ALS is relatively limited, particularly with regard to longer-term treatment proposed for patients with ALS. A total of 349 patients received edaravone in the ALS clinical trial program, including 306 subjects who received edaravone for at least 6 treatment cycles, and 98 subjects who received edaravone for at least 12 treatment cycles. 184 patients received edaravone on placebo-controlled ALS studies. The placebo-controlled phases of the ALS studies

⁵ EU Guideline, Points to consider on application with one pivotal study.

were of 24 weeks duration (6 cycles). The ALS safety dataset is supported by safety data from AIS and SAH studies, as well as post-marketing safety data relating to treatment of AIS in Japan, but treatment in the non-ALS indications is limited to 14 days duration, therefore is of limited relevance to longer-term safety.

Whilst there are limitations in the safety dataset, the ALS clinical program did not identify major safety signals of concern. In the placebo-controlled ALS safety dataset, the overall incidences of AEs, drug-related AEs, and SAEs were similar between the edaravone and placebo groups. The most frequently reported AEs by PT (edaravone greater than placebo) were contusion, gait disturbance, headache, eczema, dermatitis contact, respiratory disorder, rash, glucose urine present, and upper respiratory tract inflammation. The majority of AEs were of mild severity, and discontinuations due to AEs were less frequent in the edaravone group than placebo. The clinical significance of glycosuria findings in the ALS studies remains uncertain as blood glucose and HbA1c were not monitored in the ALS studies.

Hypersensitivity reactions, including anaphylaxis and shock, have been identified as clinically significant ADRs associated with edaravone treatment, based on post-marketing experience in AIS patients in Japan. One case of shock was reported in the ALS studies, and post-marketing safety reviews have identified additional cases of anaphylactic reaction/shock. Hypersensitivity reactions and anaphylaxis have been included in a precaution in section 4.4 of the draft Product Information and are listed in the Summary of Safety Concerns in the RMP.

The non-clinical evaluation raised concern regarding a potential risk of treatment-related neurotoxicity. The ALS clinical studies did not identify a safety signal for treatment-related neurotoxicity, but there are limitations in the capacity of the ALS clinical study program to exclude treatment-related neurotoxicity.

The ALS studies did not raise safety concerns with regard to hepatic toxicity or renal toxicity. However, in the section 31 response, the Sponsor presented a safety report which identified three *Important Potential Risks* based on review of post-marketing AIS experience in Japan:

- Worsening of hepatic function, Hepatitis.
- Worsening of renal impairment, Acute renal failure.
- Anaphylactoid reaction.

The first two *Important Potential Risks* have not yet been included in the Safety of Summary Concerns and the Sponsor addressed these two risks with the following response:

“Worsening of hepatic function, Hepatitis” and “Worsening of renal impairment Acute renal failure” were considered important potential risks at the time of submission to FDA. However, they were re-evaluated internally in December 2017 and restricted to AIS. The reasons are as follows:

- *Evidence of and “Worsening of renal impairment Acute renal failure” in the current Important Potential Risk was found in only the post marketing data of AIS.*
- *There is no evidence in all data of ALS indication including post marketing data (Japan, Korea, US).*

These are therefore considered as AIS specific Important Potential Risk, based on ALS safety profile from clinical trial data and post marketing experience.

Whilst there are limitations in the submitted safety dataset, the presented safety data support an acceptable safety profile for edaravone in the treatment of patients with ALS”.

Proposed dose

The proposed dosage of edaravone for ALS is 60 mg (two ampoules) diluted with approximately 100 mL of 0.9% sodium chloride, administered as an intravenous infusion over 60 minutes according to the following schedule:

- an initial treatment cycle with daily dosing for 14 days, followed by 14 days of no treatment.
- subsequent treatment cycles with daily dosing for 10 of the first 14 days, followed by 14 days of no treatment.

The submission did not include a robust scientific justification for the regular interruptions to treatment in the proposed dosing regimen, which appear to have been included for pragmatic and logistical reasons. The clinical impact of the regular interruptions to treatment on efficacy remains uncertain.

In response to the evaluator's concerns regarding dose selection in ALS and uncertainty regarding the impact of the treatment-free days on efficacy, the Sponsor provided the following comments:

"The Sponsor acknowledges that treatment regimen for ALS has not been examined in the edaravone program.

Immediately after edaravone was approved as a treatment of cerebral infarction in 2001, Dr. Yoshino investigated the efficacy of edaravone for ALS in an investigator-initiated clinical study. As a result, the drug was expected to be effective, and therefore, a clinical study was conducted under the initiative of the company using the same regimen for ALS.

As a point of consideration at the time, the treatment regimen approved for cerebral infarction (60 mg/day for 14 days) was used because early confirmation of efficacy was needed to deliver it to ALS patients early. Also, since the number of patients was limited, confirmation of treatment regimen was not conducted.

As indicated previously, the fact that 3NT⁶ also decreased with this regimen helped.

In order to solve this problem, a post-approval commitment study that FDA requested is currently ongoing in ALS patients using oral edaravone to compare daily edaravone with the 2 weeks ON/OFF (current regimen), and based on the results, the optimal regimen for ALS patients would be identified."

Uncertainties and limitations of the data

Concerns arising from the non-clinical evaluation include limited evidence of efficacy and a potential risk of drug-associated nerve damage.

Dose-finding for patients with ALS was limited. The dosage regimens evaluated in the Phase 2 study (Study 12) were derived from experience in AIS and included treatment-free periods of 14 days in the initial 28-day treatment cycle and 18 days in each subsequent 28-day treatment cycle. The treatment-free periods appear to have been chosen based on pragmatic considerations relating to long-term daily IV administration rather than a specific pharmacologic rationale. The impact of the treatment-free periods on efficacy remains uncertain.

Only one of the four Phase 3 ALS studies met its primary endpoint (Study 19). The initial confirmatory study (Study 16), its extension study (Study 17), and a Phase 3 study in patients with Grade 3 ALS (Study 18) all failed to demonstrate a benefit with edaravone compared to placebo.

Study 19, the pivotal study in this submission, demonstrated a benefit with edaravone compared to placebo for the primary endpoint (a significant reduction in the decline in ALSFRS-R score

⁶ 3-nitrotyrosine

over 6 cycles of treatment), but the secondary efficacy endpoints did not consistently support a treatment benefit and no adjustment was applied for multiplicity.

Study 19 evaluated the efficacy of edaravone in a restricted population based on the *definite or probable/EESP/2y* criteria from the *post-hoc* analyses of Study 16. It remains uncertain whether the efficacy findings in the restricted population evaluated in Study 19 can be extrapolated to a broader population of patients with ALS. When efficacy was examined in a broader population of patients with Grade 1 to 2 ALS in the initial confirmatory study, Study 16, no benefit was demonstrated. In addition, *post hoc* analyses of Study 16 showed a trend towards poorer outcomes in non-EESP patients treated with edaravone compared to placebo.

The findings from Study 19 have not been replicated in another study. The findings from Study 16 raise concern regarding the generalisability of the efficacy findings from Study 19.

No survival benefit has been demonstrated for edaravone. The TGA-adopted *CHMP Guideline on clinical investigation of medicinal products for the treatment of ALS* advises that survival should be assessed as a key efficacy endpoint in confirmatory trials of disease-modifying therapies. The two confirmatory studies were not designed with a statistically robust survival endpoint as a key endpoint, and neither of the studies was able to demonstrate a survival benefit. The CHMP Guideline advises that “*study duration of 12-18 months may be sufficient*”. The double-blind period in each of the confirmatory studies was only 24 weeks duration, so it is possible that the confirmatory studies were not of adequate duration to detect a survival benefit. The failure to demonstrate a survival benefit remains a notable limitation of the clinical program for edaravone.

The clinical significance of glycosuria findings in ALS studies is uncertain as blood glucose and glycated haemoglobin (HbA1c) were not monitored in the ALS studies. The Sponsor indicated that the lack of monitoring of blood glucose and HbA1c in the ALS studies was based on experience in AIS. The risk of an effect on glucose metabolism with longer-term use of edaravone in ALS has not been adequately addressed.

Proposed indication

The initial proposed indication was:

Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

In response to the round 1 clinical evaluation, the Sponsor submitted a revised indication:

Radicava (edaravone) is indicated to slow the loss of function in patients with amyotrophic lateral sclerosis (ALS), as measured by the ALS Functional Rating Scale - Revised (ALSFRS-R). Treatment should be initiated in patients with mild and moderate disabilities.

It is unclear how this revised indication addresses the concerns regarding the limited evidence of efficacy in a restricted population in Study 19, the lack of benefit in a broader population of patients with Grade 1 or 2 ALS in Study 16, and the lack of benefit in patients with Grade 3 ALS in Study 18.

In response to the round 2 clinical evaluation, the Sponsor submitted a revised indication reflecting the restrictive criteria used to define the population evaluated in Study 19:

Radicava is indicated in adults with a diagnosis of “definite” or “probable” amyotrophic lateral sclerosis (revised El Escorial criteria, ALSFRS-R scores ≥ 2 on all 12 items, FVC $\geq 80\%$, disease duration ≤ 2 years) and who have experienced a recent progression (ALSFRS score decline of 1-4 points) to delay functional decline.

Efficacy has not been demonstrated in patients outside of this defined population.

This indication aligns with the restricted population evaluated in Study 19, but the delegate is concerned that this approach does not adequately address the concern regarding the deficiencies and limitations of the efficacy data.

Proposed conditions of registration

At this stage, the delegate is not proposing to approve the registration of edaravone. If a decision is made to approve the registration of edaravone, the RMP evaluator recommendations regarding conditions of registration outlined below would apply.

Recommendation following the clinical evaluation

ALS is a devastating condition and there is an unmet need for treatments which can alter the course of the disease. My primary concern with this application relates to deficiencies and limitations of the efficacy data. The delegate is concerned that the efficacy findings from the single positive study, Study 19, are not sufficiently robust to support the registration of edaravone. Study 19 met its primary endpoint, showing a significant reduction in the decline in ALSFRS-R score compared to placebo over 6 cycles of treatment. Whilst this suggests a benefit in delaying functional decline, no survival benefit was demonstrated and the other secondary endpoints did not consistently show a benefit and were not statistically robust. The failure to demonstrate a benefit in survival and the inconsistent findings for other secondary outcomes raise concern that the efficacy findings from one pivotal study are not sufficiently robust to support registration.

Study 19 assessed efficacy in a restricted population based on the *definite or probable/EESP/2y* criteria identified in *post hoc* analyses of Study 16: “definite” or “probable” ALS diagnosis (revised El Escorial criteria), each item of the ALSFRS-R score ≥ 2 , %FVC $\geq 80\%$, and disease duration < 2 years. When efficacy was examined in a broader population of patients with Grade 1 to 2 ALS in Studies 16 and 17, no benefit in functioning or survival was demonstrated. Similarly, no benefit in functioning or survival was demonstrated in patients with Grade 3 ALS in Study 18.

In response to concerns regarding the limitations of the efficacy dataset, the Sponsor has revised the proposed indication to align with the restricted population evaluated in Study 19. However, the delegate is concerned that this is an artificially defined sub-population without a clear scientific rationale to support efficacy in this sub-population and not in a broader population. The delegate is also concerned that this approach does not adequately address the deficiencies and limitations of the efficacy dataset.

The delegate would like to consider expert advice from ACM before finalising a decision, but at this stage the delegate is of the view that the evidence of efficacy is not sufficient to support the registration of edaravone.

Risk management plan

The application included Core-RMP version 1.1 (date 11 May 2021; DLP 4 November 2017) and ASA version 1.0 (date 14 September 2021), plus ASA version 1.1 (date 26 May 2022) submitted at Round 2. The summary of safety concerns and their associated risk monitoring and mitigation strategies are presented in Table 46. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 46: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	✓	-	✓	-
Important potential risks	Hypersensitivity reaction, anaphylactic reaction	✓	-	✓	-
	Use in pregnancy and lactation*	✓	-	✓	-
Missing information	Patients with ALS severity grade > 3 and/or decreased respiratory function (%FVC < 80%)	✓	✓ ¹	✓	-
	Long-term safety (> 12 cycles)*	✓	-	✓	-
	Use in patients over 75 years*	✓	-	✓	-
	Use in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m ²)*	✓	-	✓	-

¹ Ongoing observational studies: Japan Survey (Observation for safety under actual drug use in ALS severity > 3); South Korean Survey (Surveillance for safety in ALS severity > 3).

*Australia-specific safety concerns

RMP evaluator recommendations regarding conditions of registration:

- The Radicava Core-RMP (version 1.1, dated 11 May 2021, data lock point 04 November 2017), with Australian Specific Annex (version 1.1, dated 26 May), included with submission PM-2021-04298-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
- Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the Sponsor wishes, the six-monthly reports may be submitted separately as they become available.
- If the product is approved in the EU during the three years period, reports can be provided in line with the published list of EU reference dates no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.
- The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Edaravone (Radicava) is to be included in the Black Triangle Scheme. The PI and CMI for Radicava must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the Sponsor notifies the TGA of supply of the product.

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in [risk management plans for medicines and biologicals](#) and [the TGA's risk management approach](#). Information on the [Australia-specific annex \(ASA\)](#) can be found on the TGA website.

Advisory Committee considerations

The [Advisory Committee on Medicines \(ACM\)](#), having considered the evaluations and the Delegate's overview, as well as the Sponsor's response to these documents, advised the following.

9. What is ACM's advice regarding the evidence of efficacy of edaravone in ALS?

The ACM was of the view that a modest functional benefit has been demonstrated for edaravone within the population included within Study 19.

The ACM noted that only one (study 19) of the four Phase 3 studies demonstrated a statistically significant reduction in decline within the ALSFRS-R score. The ACM also noted more broadly that published data demonstrated mixed results. Some reassurance was provided by data from an open label study that showed the maintenance of reduction in decline in the ALSFRS-R score remained evident at 48 weeks. The ACM noted that the modest treatment benefit observed in Study 19 was also seen in the open-label extension of Study 19 as well as the post-hoc analysis of Study 16.

The ACM noted there was no effect on respiratory function, grip and pinch strength nor was an improvement in overall survival demonstrated. The ACM expressed some concern regarding the modest magnitude of the function only effect and queried the mechanism of action noting that there does not appear to be any impact on muscle strength.

The ACM discussed whether a reduction in the decline in the ALSFRS-R score equates to realised patient benefit and was of the view that the patient outcome would potentially be that their ALS does not progress as fast as expected.

The ACM highlighted that efficacy was only demonstrated within the bounds of the inclusion criteria of Study 19 (ALS grade 1-2, disease duration of ≤ 2 years, who remained independent in ADLs and had $\geq 80\%$ predicted FVC). The ACM highlighted the importance of restricting use to those with a disease duration of ≤ 2 years noting that efficacy was not demonstrated in the clinical study with an inclusion criteria of disease duration of ≤ 3 years. The ACM agreed that Australian neurologists would be able to identify relevant patients (disease duration ≤ 2 years) however did express some concern regarding prescribing outside the approved indication and advised that the PI clearly highlight the limitations of the clinical data.

Noting the lack of efficacy beyond ALS grade 2 the ACM discussed whether it is appropriate to discontinue treatment once a patient progresses beyond grade 2. The ACM commented that there is currently uncertainty within this space and limited information to guide discontinuation.

10. What is ACM's view regarding the lack of a demonstrated benefit on survival?

The ACM was of the view that a demonstrated benefit on survival would have been preferred, however, noted that the demonstrated preservation of function has value.

The ACM noted that the demonstration of survival benefit is an important component of the CHMP guideline for drugs for ALS. However, the ACM acknowledged that this guideline was developed and adopted after the Sponsor's clinical studies on edaravone were conducted.

The ACM agreed that the PI (and CMI) should clearly state that a benefit on survival has not been demonstrated, as this statement would assist patients and prescribers to make an informed decision.

11. What is ACM's opinion regarding the Sponsor's initially proposed indication for the treatment of ALS?

The ACM noted the initially proposed indication edaravone is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

The ACM was of the view that this wording is too broad and does not align with the clinical study data which suggest a modest benefit in early stages of disease only.

12. What is ACM's opinion regarding the Sponsor's revised indication with a restricted population based on the criteria used in Study 19?

The ACM noted the revised indication:

Radicava is indicated in adults with a diagnosis of "definite" or "probable" amyotrophic lateral sclerosis (revised El Escorial criteria, ALSFRS-R scores ≥ 2 on all 12 items, FVC $\geq 80\%$, disease duration ≤ 2 years) and who have experienced a recent progression (ALSFRS score decline of 1-4 points) to delay functional decline.

Efficacy has not been demonstrated in patients outside of this defined population.

The ACM noted the inclusion of 'definite or probable ALS' and diagnostic tests and scores in the proposed indication. The ACM advised these diagnostic criteria are becoming obsolete, being replaced by the Gold Coast criteria. Based on this the ACM recommended simpler language to describe the patient group, such as 'diagnosis of ALS and independent in activities of daily living with normal respiratory function' and disease duration ≤ 2 years.

The ACM noted the use of the Japan ALS severity classification in the clinical studies and reiterated that efficacy has only been demonstrated within ALS grades 1 and 2 and this should be clearly outlined within the PI. The ACM advised that this could be described in the indication as patients 'who are independent in activities of daily living'.

The ACM highlighted the importance of stating within the PI that Efficacy has not been demonstrated in patients outside of this defined population and noted that this wording would assist patients and prescribers to make an informed decision on treatment.

On balance the ACM noted the modest functional benefit of treatment for the defined patient group in addition to a continued need for effective ALS treatments and was of the view that the indication with amendments is appropriate. The ACM further acknowledged that these patients would be treated in tertiary centres by specialists with expertise in ALS.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

Radicava is indicated in adults with a diagnosis of amyotrophic lateral sclerosis who are independent in activities of daily living with normal respiratory function and where treatment is initiated within two years of disease onset.

Efficacy has not been demonstrated in patients outside of this defined population.

Risk/benefit assessment (post-Advisory Committee Meeting)

The Delegate, as well as the ACM, recognised the limitations of the clinical dataset, particularly in relation to efficacy. However, the Delegate acknowledged the advice of the clinical experts that the modest benefit on functional decline was clinically meaningful, particularly in the context of very limited treatment options available to patients with ALS. The ACM advised that the indication should be restricted to the population in which efficacy has been demonstrated and preferred that this be expressed with simpler wording. In light of this expert advice, the Delegate is inclined to proceed with approval and the indication recommended by the ACM.

Outcome

Based on a review of quality, safety, and efficacy data, the TGA decided to register Radicava. The approved indication for this therapeutic good is:

Radicava is indicated in adults with a diagnosis of amyotrophic lateral sclerosis who are independent in activities of daily living with normal respiratory function and where treatment is initiated within two years of disease onset.

Efficacy has not been demonstrated in patients outside of this defined population.

Attachment 1. Product Information

The [Product Information \(PI\)](#) approved with the submission for Radicava which is described in this AusPAR can be accessed on the Radicava AusPAR home page on the TGA website. It may have been superseded. For the most recent PI and [Consumer Medicines Information \(CMI\)](#), please refer to the TGA [PI/CMI search facility](#).

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