Report on the Deliberation Results

June 11, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

[Brand name] (a) Radicut Injection 30 mg
(b) Radicut Bag for Intravenous Infusion 30 mg

[Non-proprietary name] Edaravone (JAN*)

[Name of applicant] Mitsubishi Tanabe Pharma Corporation

[Date of application] October 29, 2014

[Review results]

In the meeting held on June 5, 2015, the First Committee on New Drugs concluded that the partial change application for the products may be approved and that the review results should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period of the products is 10 years.

[Conditions for approval]

The applicant is required to develop a risk management plan and implement it appropriately.

On the basis of the deliberation at the Committee, the statements of the dosage and administration have been modified as shown below. This modification does not affect other review results.

After modification	Before modification
[Dosage and Administration] (a) Radicut Injection 30 mg: 1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairement associated with acute ischemic stroke The usual adult dosage is 30 mg of edaravone (1 ampoule) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening. Edaravone should be diluted with an appropriate volume of normal saline or other suitable diluent prior to administration. Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days. 2. Slowing of progression of functional impairement in patients with amyotrophic	[Dosage and Administration] (a) Radicut Injection 30 mg: 1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairement associated with acute ischemic stroke The usual adult dosage is 30 mg of edaravone (1 ampoule) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening. Edaravone should be diluted with an appropriate volume of normal saline or other suitable diluent prior to administration. Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days. 2. Slowing of progression of functional impairement in patients with amyotrophic

lateral sclerosis (ALS) The usual adult dosage is 60 mg of edaravone (2 ampoules) administered once daily by intravenous infusion over 60 minutes. Edaravone should be diluted with an appropriate volume of normal saline or other suitable diluent prior to administration. Usually, edaravone should be administered in 28-day cycles, each consisting of a treatment period and a rest period. In the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day treatment period, followed by a 14-day rest period.	lateral sclerosis (ALS) The usual adult dosage is 60 mg of edaravone (2 ampoules) administered once daily by intravenous infusion over 60 minutes. Edaravone should be diluted with an appropriate volume of normal saline or other suitable diluent prior to administration. Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. Usually, in the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day period, followed by a 14-day rest period.
(b) Radicut Bag for Intravenous Infusion 30 mg: 1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairement associated with acute ischemic stroke The usual adult dosage is 30 mg of edaravone (1 bag) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening. Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days. 2. Slowing of progression of functional impairement in patients with amyotrophic lateral sclerosis (ALS) The usual adult dosage is 60 mg of edaravone (2 bags) administered once daily by intravenous infusion over 60 minutes. Usually, edaravone should be administered in 28-day cycles, each consisting of a treatment period and a rest period. In the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day treatment period, followed by a 14-day rest period.	(b) Radicut Bag for Intravenous Infusion 30 mg: 1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairement associated with acute ischemic stroke The usual adult dosage is 30 mg of edaravone (1 bag) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening. Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days. 2. Slowing of progression of functional impairement in patients with amyotrophic lateral sclerosis (ALS) The usual adult dosage is 60 mg of edaravone (2 bags) administered once daily by intravenous infusion over 60 minutes. Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. Usually, in the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day period, followed by a 14-day rest period.

(Modified parts are underlined.)

**Japanese Accepted Name (modified INN)*

Review Report

May 19, 2015
The Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical products submitted for registration are as follows.

[Brand name]	(a) Radicut Injection 30 mg (b) Radicut Bag for Intravenous Infusion 30 mg
[Non-proprietary name]	Edaravone
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	October 29, 2014
[Dosage form/Strength]	(a) Injection: Each 20 mL ampoule contains 30 mg of edaravone. (b) Injection: Each 100 mL bag contains 30 mg of edaravone.
[Application classification]	Prescription Drugs; (4) Drugs with a new indication, (6) Drugs with a new dosage
[Items warranting special mention]	Orphan drug (Designation number [17 yaku] No. 180, Notification No. 0620004 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW; dated June 20, 2005)
[Reviewing office]	Office of New Drug III

Review results

May 19, 2015

[Brand name]	(a) Radicut Injection 30 mg
	(b) Radicut Bag for Intravenous Infusion 30 mg
[Non-proprietary name]	Edaravone
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	October 29, 2014

[Review results]

Based on the data submitted by the applicant, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the slowing of progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS) has been demonstrated, and that the safety is acceptable in view of their benefits.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the following indications and dosage and administration, with the following conditions for approval.

[Indications]

1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke
2. Slowing of progression of functional impiarment in patients with amyotrophic lateral sclerosis (ALS)

(The underlined text denotes additions in this application.)

[Dosage and administration]

(a):

1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke

   The usual adult dosage is 30 mg of edaravone (1 ampoule) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening. Edaravone should be diluted with an appropriate volume of normal saline or other suitable diluent prior to administration.

   Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days.
2. Slowing of progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS)

The usual adult dosage is 60 mg of edaravone (2 ampoules) administered once daily by intravenous infusion over 60 minutes. Edaravone should be diluted with an appropriate volume of nomal saline or other suitable diluent prior to adminitration.

Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. Usually, in the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day period, followed by a 14-day rest period.

(b):

1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke

   The usual adult dosage is 30 mg of edaravone (1 bag) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening.

   Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days.

2. Slowing of progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS)

   The usual adult dosage is 60 mg of edaravone (2 bags) administered once daily by intravenous infusion over 60 minutes.

   Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. Usually, in the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day period, followed by a 14-day rest period.

(The underlined text denotes additions in this application.)

[Conditions for approval] The applicant is required to develop a risk management plan and implement it appropriately.

Review Report (1)

March 27, 2015

I. Products submitted for registration

[Brand name]	(a) Radicut Injection 30 mg (b) Radicut Bag for Intraveous Infusion 30 mg
[Non-proprietary name]	Edaravone
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	October 29, 2014
[Dosage form/Strength]	(a) Injection: Each 20 mL ampoule contains 30 mg of edaravone. (b) Injection: Each 100 mL bag contains 30 mg of edaravone.
[Proposed indications]	1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke 2. Treatment of amyotrophic lateral sclerosis (ALS) Slowing of progression of amyotrophic lateral sclerosis (ALS) Slowing of deterioration of the quality of life (QOL) (e.g., walking, activities of daily living, speech, anxiety) associated with amyotrophic lateral sclerosis (ALS) (The underlined test denotes additions in this application.)
[Proposed dosage and administration]	(a): 1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke The usual adult dosage is 30 mg of edaravone (1 ampoule) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening. Edaravone should be diluted with an appropriate volume of nomal saline or other suitable diluent prior to administration. Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days. 2. Treatment of amyotrophic lateral sclerosis (ALS) Slowing of progression of amyotrophic lateral sclerosis (ALS) Slowing of deterioration of the quality of life (QOL) (e.g., walking, activities of daily living, speech, anxiety) associated with amyotrophic lateral sclerosis (ALS) The usual adult dosage is 60 mg of edaravone (2 ampoules) administered once daily by intravenous infusion over 60

minutes. Edaravone should be diluted with an appropriate volume of nomal saline or other suitable diluent prior to administration.

Edaravone should be administered for up to 14 days, followed by a 14-day rest period. Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. In the first cycle, edaravone should be administered for 14 consecutive days. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day period.

(b):

1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke

   The usual adult dosage is 30 mg of edaravone (1 bag) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening.

   Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days.

2. Treatment of amyotrophic lateral sclerosis (ALS)

   Slowing of progression of amyotrophic lateral sclerosis (ALS)
   Slowing of deterioration of the quality of life (QOL) (e.g., walking, activities of daily living, speech, anxiety) associated with amyotrophic lateral sclerosis (ALS)

   The usual adult dosage is 60 mg of edaravone (2 bags) administered once daily by intravenous infusion over 60 minutes.

   Edaravone should be administered for up to 14 days, followed by a 14-day rest period. Edaravone should be should be administered in cycles, each consisting of a treatment period and a rest period.

   In the first cycle, edaravone should be administered for 14 consecutive days. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day period.

(The underlined text denotes additions in this application.)

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

This partial change application has been submitted for a new indication and a new dosage of the already approved drug product. While the maximum recommended treatment duration is 14 days for the existing indication (i.e., improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke), none is specified for the proposed new indications. However, no additional data from toxicity studies were submitted for the "Non-clinical data" section in this application because the safety of long-term intermittent treatment with the product has been substantially confirmed with the following findings: (1) The results of 30-day and 26-week repeat-dose toxicity studies in rats and dogs submitted in the new drug application for the existing indication showed no toxicology findings associated with a longer duration of treatment; and (2) no carcinogenicity was observed in carcinogenicity studies in mice and rats conducted by the National Cancer Institute of the United States (Bioassay of 1-phenyl-3-methyl-5-pyrazolone for possible carcinogenicity, *National Cancer Institute Carcinogenesis Technical Report Series.* 1978;*No.141*).

1. Origin or history of discovery and usage conditions in foreign countries etc.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by sporadic degeneration or loss of upper and lower motor neurons, and causes generalized muscle atrophy and weakness. The median time from onset to death or the introduction of invasive ventilation has been reported to range from 20 to 48 months. In Japan, the incidence rate of ALS is estimated to range from 1.1 to 2.5 per 100,000 person-years, and the prevalence of ALS is estimated to range from 7 to 11 per 100,000 persons. ALS is most common among people in their 60s and 70s, and the incidence of ALS is 1.3- to 1.4-fold greater in men than in women (the Japanese Society of Neurology, *Practical Guidelines for Amyotrophic Lateral Sclerosis 2013*;2013).

Edaravone (hereinafter referred to as “edaravone”), the active ingredient of Radicut Injection 30 mg and Radicut Bag for Intravenous Infusion 30 mg (hereinafter collectively referred to as "Radicut"), is a free radical scavenger discovered by Mitsubishi Yuka Pharmaceutical Co., Ltd. (currently, Mitsubishi Tanabe Pharma Corporation) in 1984. In Japan, Radicut Injection 30 mg was approved in April 2001, and Radicut Bag for Intravenous Infusion 30 mg in January 2010, for the indication of "improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke." As of March 2015, Radicut is not marketed outside Japan.

The applicant began clinical trials as the clinical development program for the use of edaravone in ALS patients in [redacted] 20[redacted]. With the claim that the efficacy and safety of edaravone (Radicut) in the treatment

of ALS have been demonstrated, the applicant has submitted partial change application for the approved product. Edaravone (Radicut) was designated as an orphan drug on June 20, 2005 with the expected indication for the treatment of ALS (Designation No. [17 yaku] No. 180).

In Japan, riluzole has been approved for the "treatment of amyotrophic lateral sclerosis (ALS)" and "slowing of progression of amyotrophic lateral sclerosis (ALS)."

2. Non-clinical data

2.(i) Summary of pharmacology studies

2.(i).A. Summary of the submitted data

2.(i).A.(1) Primary pharmacodynamics (4.2.1.1-1)

Transgenic mice expressing a mutant superoxide dismutase (SOD) gene[1)] were given vehicle (nomal saline) or edaravone at a dose of 3 mg/kg/day by intravenous infusion over 1 hour in cycles of 2-day treatment and 2-day rest periods during the period from 18 weeks of age to the day of death.[2)] The median survival times in male and female animals were 205 and 215 days, respectively, in the vehicle control group and were 201 and 212 days, respectively, in the edaravone group, with no statistically significant difference between the 2 treatment groups in either sex. In the inclined plate test,[3)] the decrease in the tilt angle of an inclined plate at the age of 30 to 32 weeks was significantly suppressed in female animals in the edaravone group than in matched animals in the control group.[4)] Comparisons of the time to death,[5)] body weight, hind-foot reflex test score,[6)] landing foot-splay,[7)] rotarod performance time,[8)] and the number of viable bone marrow cells[9)] did not reveal any significant differences between the edaravone and control groups.

2.(i).B Outline of the review by PMDA

PMDA asked the applicant to explain the mechanism of action of edaravone in the light of the pathophysiology of amyotrophic lateral sclerosis (ALS).

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1) It has been reported that approximately 20% of patients with familial ALS have mutations in a gene that encodes Cu/Zn-binding superoxide dismutase (SOD1), an enzyme that scavenges free radicals (Rosen DR, et al., *Nature*. 1993;362:59-62, Nagai M, et al., *Kitasato Medicine*. 2012;42:85-93). Transgenic mice with an H46R mutant SOD1 gene, one of the commonly reported ALS-related mutations, show loss of motor neuron and decrease in motor activity. The mice are considered as an animal model of ALS (Nagai M, et al., *J. Neurosci*. 2001;21:9246-9254).

2) The day of loss of righting reflex was defined as the day of death.

3) The maximum tilt angle of an inclined plate at which the animals, placed along the slope with the head at the top, remained on the plate for at least 5 seconds was recorded.

4) The significant difference tests for inclined plate angle, hind-foot reflex, landing foot-splay, and rotarod performance time was conducted at a total of 5 time points, consisting of the closest earlier time point to the day by which 50% of animals in the control group died, and 2 time points each immediately before and after it.

5) Defined as the number of days from the day a hind-foot reflex score[6)] become 1 (day of onset) to the day of death.

6) The animal was hung by its tail to rate the extension of the extremities (Score 0 = complete extension of the extremities; 1 = flexion of 1 of the extremities; 2 = flexion of 2 of the extremities; 3 = flexion of 3 of the extremities; 4 = flexion of all extremities.)

7) The animal, held parallel to the surface, was dropped on a surface from a 30 cm height, and the distance between the hind legs was measured.

8) The duration of stay on the rotarod with a 9 cm diameter, rotating at 5 rpm, was measured.

9) Spinal sections at the L3 level were prepared at 26 weeks of age for males and 28 weeks of age for females. Sections were stained with the Nissl staining to determine viable cell count.

The applicant explained as follows:

ALS is a neurodegenerative disease characterized by selective degeneration and loss of motor neurons, which causes progressive, generalized muscle atrophy. Several hypotheses have been proposed on the mechanism of the degeneration of motor neurons, including dysfunction of mitochondria, protein aggregation, and endoplasmic reticulum stress.[10)] It has also been reported that 3-nitrotyrosine (3-NT), 8-oxo-deoxyguanosine, and 4-hydroxynonenal levels, which serve as markers of oxidative modification of proteins, DNA, and lipids, respectively, are found at increased concentrations in the spinal cord, cerebrospinal fluid, plasma, etc. of patients with familial ALS and sporadic ALS.[11)] These findings suggest that free radical-mediated oxidative stress plays a role in the degeneration of motor neurons.

In vitro studies of edaravone have revealed that the drug scavenges hydroxyl radicals and prevents the peroxidation of lipids and glutamate-induced neuronal death in cultured rat neurons (according to the data/information submitted in the initial new drug application). In addition, edaravone is reported to have inhibited the generation of H_2O_2-induced reactive oxygen species and apoptosis of cultured rodent neurons as well as glutamate-induced endoplasmic reticulum stress and apoptosis (Zhao ZY, et al., *CNS Neurosci Ther*. 2013;19:163-169, Fan J, et al., *Brain Res.* 2013;1519:1-8). In the phase II study of edaravone (5.3.5.2-1), the 3-NT level in spinal fluid decreased in ALS patients receiving edaravone. As the effects on motor function associated with ALS, edaravone slowed down the decrease in the tilt angle in the inclined plate test with transgenic mice expressing a mutant SOD gene (4.2.1.1-1); the progression of quadriplegia and reductions in rotarod time and grip strength in transgenic mice expressing a mutant SOD1 gene (Ito H, et al., *Exp Neurol*. 2008;213:448-455); and the reductions in grip strength and muscle weight in wobbler mice[12)] (Abe K editor, *Molecular Mechanisms and Therapeutics of Amyotrophic Lateral Sclerosis*. 2001;335-340).

On the basis of the above findings, the applicant explained that edaravone prevents the generation of free radicals related to the pathophysiology of ALS in order not only to protect motor neurons from oxidative stress but also to protect motor neurons by inhibiting endoplasmic reticulum stress and apoptosis, thereby slowing down the progression of ALS.

The applicant also presented a number of recent publications reporting that glial cells and vascular endothelium affect the survival of motor neurons. Gliosis of microglia and astrocytes, injury of oligodendrocyte precursor cells (OPC), and loss of myelin were observed in the brain and spinal cord of patients with ALS (Philips T, et al., *Exp Neurol*. 2014;262:111-120); and breakdown of the blood-

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[10)] Nagai M, Kitasato Medicine, 42: 85-93, 2012; D'Amico E, et al., *Free Radic Biol Med*. 2013;65:509-527, Parakh S, et al., *Oxid Med Cell Longev*. 2013;2013:408681, Vucic S, et al., *Trends Neurosci*. 2014;37:433-442

[11)] D'Amico E, et al., *Free Radic. Biol. Med*. 2013;65:509-527, Parakh S, et al., *Oxid Med Cell Longev*. 2013;2013: Article ID 408681, Beal MF, et al, *Ann Neurol*, 1997;42: 644-654

[12)] The phenotype of the wobbler mouse is similar to that of human ALS, which is characterized by loss of motor neurons and motor dysfunction, the presence of ubiquitin-positive intraneuronal inclusions in the spinal cord, and excessive expression and aggregation of TDP-43 (transactive response DNA binding protein 43 kDa) (Dennis JS, et al., *Neurosci.* 2009;158:745-750).

spinal cord barrier was observed in patients with sporadic ALS (Garbuzova-Davis S, et al., *Brain Res.* 2012;1469:114-128). A study of transgenic mice expressing SOD1 mutations has reported that the destruction of blood-spinal cord barrier contributes to motor-neuron degeneration (Winkler EA, et al., *Proc Natl Acad Sci*. 2014;111:E1035-1042). Meanwhile, other reports showed that edaravone reduces oxidative cell death in astrocytes and vascular endothelium (Lee BJ, et al., *Brain Res*. 2010;1307:22-27, the date/information submitted in the initial new drug application), and that edaravone promotes OPC-to-oligodendrocyte differentiation by suppressing oxidative stress which disrupts OPC differentiation (Miyamoto N, et al., *Stroke*. 2013;44:3516-3521). On the basis of the above findings, the applicant explained that edaravone exerts its beneficial effects on patients with ALS not only by directly protecting motor neurons but also by reducing oxidative stress in glial cells and vascular endothelium, thereby protecting motor neurons.

PMDA accepted the above explanation, considering that the applicant discussed the mechanism of action of edaravone in the treatment of ALS as much as possible on the basis of the currently available findings, although the pathological mechanism of ALS has not been fully clarified.

3. Clinical data

3.(i) Summary of clinical pharmacology studies

3.(i).A. Summary of the submitted data

As the evaluation data, the results of *in vitro* studies of human biomaterials were submitted.

3.(i).A.(1) Studies using human biomaterials

^{14}C-edaravone was added to human serum to determine the plasma protein binding rate by the ultrafiltration method. The binding rate of ^{14}C-labeled edaravone (5.74 and 57.4 μmol/L) ranged from 92.0% to 92.8%. The binding rate of ^{14}C-edaravone (5.74 and 57.4 μmol/L) added to human serum in the presence of riluzole (0.854 and 8.54 μmol/L) ranged from 90.8% to 92.4%. Riluzole did not affect the plasma protein binding of edaravone. Also, warfarin, salicylic acid, or ticlopidine hydrochloride did not affect the plasma protein binding of edaravone (5.3.2.2-1).

Edaravone did not affect the plasma protein binding of warfarin or salicylic acid when ^{14}C-labeled warfarin (3.24 or 32.4 μmol/L) or ^{14}C-labeled salicylic acid (72.4 or 724 μmol/L) was added to human serum with or without ^{14}C-edaravone (5.74 or 57.4 μmol/L) (5.3.2.2-2).

In a study using human liver microsomes, the 50% inhibitory concentration (IC_{50}) values of edaravone against the metabolic activities of CYP2C19, CYP2D6, and CYP3A4 exceeded 1000 μmol/L, while those against the metabolic activities of CYP1A2 and CYP2C8/9 were 832.2 μmol/L and 33.4 μmol/L, respectively (5.3.2.2-3). Considering the estimated peak plasma concentration (8.4 μmol/L) of

edaravone in humans after intravenous infusion over 60 minutes at a dose of 60 mg[13] and the protein binding rate (92%) of edaravone, it is unlikely that in clinical use, edaravone inhibits CYP isoenzymes including CYP1A2, major riluzole-metabolizing enzyme.

When 60 μmol/L ^{14}C-edaravone was added to microsomes expressing human UDP-glucuronosyltransferase (UGT) enzyme system (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17), ^{14}C-edaravone was conjugated by UGT1A1, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B17 (5.3.2.2-4).

3.(i).B Outline of the review by PMDA

PMDA considered there is no particular problems in the submitted study results.

3.(ii) Summary of clinical efficacy and safety

3.(ii).A. Summary of the submitted data

As the data for evaluation of efficacy and safety, the results of exploratory studies (5.3.5.2-1, Study MCI186-12; and 5.3.5.1-4, Study MCI186-18), confirmatory studies (5.3.5.1-2, Study MCI186-16; and 5.3.5.1-1, Study MCI186-19), and an extension study (5.3.5.1-3, Study MCI186-17) in Japanese patients with ALS were submitted.

3.(ii).A.(1) Exploratory studies

3.(ii).A.(1).1) Phase II study (5.3.5.2-1, Study MCI186-12 [November 2001 to November 2002])

An open-label non-controlled study was conducted in Japanese patients with ALS (target sample size: 20 patients in total, 5 patients in the 30 mg group and 15 patients in the 60 mg group) to evaluate the safety and efficacy of intravenous edaravone.

Patients were to receive edaravone once daily by intravenous infusion over 30 minutes at a dose of 30 mg or over 60 minutes at a dose of 60 mg. The first cycle of treatment consisted of a 2-week, once-daily treatment period, followed by a 2-week rest period. From cycle 2 to 6 of treatment (i.e., a total of 5 cycles), each cycle consisted of a 2-week treatment period, during which a total of 10 doses of edaravone (5 doses/week) were administered, followed by a 2-week rest period.

Of the 20 patients enrolled in the study (5 and 15 patients in the 30 mg and 60 mg groups, respectively), 19 patients (i.e., 5 and 14 patients in the 30 and 60 mg groups, respectively) were included in the full analysis set (FAS) which was used for safety and efficacy analyses, and the remaining 1 patient in the 60 mg group was excluded from the FAS due to having a disease other than ALS. Treatment was discontinued in 4 patients (1 and 3 patients in the 30 and 60 mg groups, respectively) mainly due to the

[13] The concentration was calculated using a total clearance of edaravone (683 mL/h/kg) based on the assumption of a healthy adult male with a body weight of 60 kg (the data submitted in the initial application).

progression of ALS (1 patient each in the 30 and 60 mg groups).

The primary endpoint was the ALS Functional Rating Scale-Revised (ALSFRS-R)[14] score at week 24 of treatment. The percentage of patients who were assessed to "have a slower rate" of disease progression according to the difference in cumulative ALSFRS-R scores[15] was 20% (1 of 5) of patients in the 30 mg group and 50% (7 of 14) of patients in the 60 mg group.

Adverse events, including abnormal laboratory findings, occurred in 5 of 5 patients (100%) in the 30 mg group and in 13 of 14 patients (92.9%) in the 60 mg group. No deaths occurred. Serious adverse events other than death were observed in 3 patients in the 30 mg group (respiratory failure in 2 patients and bronchitis NOS in 1 patient) and 3 patients in the 60 mg group (bronchitis acute NOS/respiratory failure, pneumonia NOS/dysphagia, and respiratory failure in 1 patient each). A causal relationship of these events to the study drug was ruled out.[16]

Adverse events, including abnormal laboratory findings, for which a causal relationship to the study drug could not be ruled out[16] were observed in none in the 30 mg group, and 1 of 14 patients (7.1%) in the 60 mg group; this patient experienced diarrhoea NOS and loose stools.

Evaluation of vital signs (blood pressure and pulse rate) revealed an increase in blood pressure in 1 patient in the 60 mg group. Since this patient had hypertension as an underlying condition, this event was not considered an adverse event.

Based on the above, the applicant explained that there were no major problems in terms of the safety of edaravone at a dose of 30 mg or 60 mg and that the efficacy of edaravone was demonstrated in patients with ALS.

3.(ii).A.(1).2) Exploratory study in patients with grade 3 ALS according to Japanese ALS severity

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[14] The ALSFRS-R is a rating scale to assess the functional impairment including disability in activities of daily living in patients with ALS. The ALSFRS-R consists of 12 items to evaluate speech, salivation, swallowing, handwriting, cutting food, dressing and hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Each item is rated on 5-point scale from 0 to 4 (4 represents normal condition).

[15] For each patient, the investigator calculated the mean difference between the baseline ALSFRS-R score (the score immediately before the first dose of edaravone in cycle 1) and ALSFRS-R scores at 6 time points during the period from 1 to 6 months before cycle 1 ("difference in the cumulative score from the pre-baseline period"), and the mean difference between the baseline ALSFRS-R score and ALSFRS-R scores at 6 time points during the treatment period that are before the first doses in cycles 2 to 6, and 2 weeks after the final dose in cycle 6 ("difference in the cumulative score during the study period"). The efficacy of treatment was rated on the basis of the ratio of difference in the cumulative score during the study period to that from the pre-baseline period as follows:
Progression was "inhibited" when the ratio was ≤50%; "slightly inhibited" when the ratio was between >50% and <100%; and "not changed" when the ratio was ≥100%.

[16] A causal relationship between the event and the study drug was rated on a 4-grade scale of "not related," "unlikely," "possible," and "probable." Adverse events rated as "possible" or "probable" were defined as adverse events for which a causal relationship cannot not be ruled out, and those rated as "not related" or "unlikely" were defined as adverse events for which a causal relationship can be ruled out.

classification (5.3.5.1-4, Study MCI186-18 [December 2006 to July 2008])

In order to evaluate the efficacy and safety of edaravone in Japanese patients with grade 3 ALS according to the Japanese ALS severity classification,[17] a placebo-controlled, double-blind, parallel group comparison study was conducted (target sample size: 10 patients for each group).

Patients were to receive placebo or edaravone at a dose of 60 mg once daily by intravenous infusion over 60 minutes. The first cycle of treatment consisted of a 2-week daily treatment period followed by a 2-week rest period. From cycles 2 to 6 of treatment (i.e., a total of 5 cycles), each cycle consisted of a 2-week treatment period, during which a total of 10 doses of the study drug were administered, followed by a 2-week rest period.

All of the 25 patients randomized for the study (i.e., 12 and 13 patients in the placebo the edaravone groups, respectively) were included in the full analysis set (FAS) which was used for efficacy and safety analyses. The study was discontinued in 4 patients (0 and 4 in the placebo and edaravone groups, respectively) due to the patient's request (2 patients), occurrence of adverse events (1 patient), and impossible continuation of the study due to the patient's personal reasons (1 patient).

The primary efficacy endpoint was the change in ALSFRS-R score from baseline (immediately before the first dose in cycle 1) to 2 weeks after the final dose in cycle 6 or at the time of study discontinuation (the last-observation-carried-forward [LOCF] method) in the FAS.[18] The data are summarized in Table 1.

Table 1. Change in ALSFRS-R score in Study MCI186-18 (FAS, LOCF)

Group	No. of patients evaluated	ALSFRS-R score[a]		Change[b) c)]	Comparison with placebo[c]	
		Before cycle 1 of treatment	2 weeks after the final dose in cycle 6 or at discontinuation (LOCF)		Difference between the groups[d]	P value
Placebo group	12	34.6 ± 3.3	29.2 ± 4.9	-6.00 ± 1.83	-0.52 [-5.62, 4.58]	0.8347
Edaravone group	13	32.5 ± 5.5	26.6 ± 9.9	-6.52 ± 1.78		

a) Mean ± standard deviation
b) Adjusted mean ± standard error
c) Based on an analysis of variance model using treatment group and the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4) as factors.
d) Radicut group minus placebo group (95% confidence interval [CI])

Adverse events, including abnormal laboratory findings, were observed in 12 of 12 patients (100%) in

[17] The Japanese ALS severity classification score (according to the severity classification of the ALS Clinical Research Form prepared by the Ministry of Health, Labor and Welfare of Japan)
1: able to work or perform housework on the whole
2: able to make an independent living but having difficulty in working or performing housework
3: requiring assistance for daily living, and unable to do 1 or more of eating, excretion, and ambulation, independently
4: presence of respiratory insufficiency/difficulty in coughing up sputum, or dysphagia
5: using tracheostomy, parenteral nutrition administration (e.g., tubal feeding, and central venous nutrition) or ventilator use

[18] When the change in ALSFRS-R score was calculated, missing data at 2 weeks after the final dose in cycle 6 were replaced by the last observed value (the LOCF method). However, this method was to be applied only to patients who completed study treatment at least by the end of cycle 3 (i.e., day 81 of treatment).

the placebo group, and in 12 of 13 patients (92.3%) in the edaravone group. One patient in the edaravone group died of respiratory failure, but the investigator concluded that the patient died due to the progression of ALS, and ruled out a causal relationship between the death and the study drug.[16] Serious adverse events other than death were observed in 2 patients in the placebo group (musculoskeletal disorder and pelvic venous thrombosis in 1 patient each) and 3 patients in the edaravone group (dysphagia/gait disturbance/musculoskeletal disorder, dyspnoea, and dysphagia in 1 patient each). A causal relationship between these events and the study drug was ruled out.[16]

Adverse events, including abnormal laboratory findings, for which a causal relationship to the study drug could not be ruled out[16] were observed in 1 of 12 patients (8.3%) in the placebo group (haemorrhage subcutaneous), and 3 of 13 patients (23.1%) in the edaravone group (muscular weakness, feeling cold, and rash in 1 patient each).

No systematic evaluation of vital signs or electrocardiogram were made in the study.

Based on the above, the applicant explained that the efficacy of edaravone could not be confirmed in patients with a Japanese ALS severity classification score of 3, but that there were no major problems in terms of safety.

3.(ii).A.(2) Confirmatory studies

3.(ii).A.(2).1) Confirmatory Study 1 (5.3.5.1-2, Study MCI186-16 [May 2006 to September 2008])

A placebo-controlled, randomized, double-blind, parallel group comparison study was conducted in Japanese patients with ALS[19),20)] (target sample size: 200 patients in total, 100 patients each in the placebo and edaravone groups) to assess the efficacy and safety of edaravone therapy.

Patients were to receive placebo or edaravone at a dose of 60 mg once daily by intravenous infusion over 60 minutes. The first cycle of treatment consisted of a 2-week daily treatment period and a 2-week rest period. In each of cycles 2 to 6 of treatment (i.e., a total of 5 cycles), a total of 10 doses of the study drug were administered during a 2-week treatment period, followed by a 2-week rest period. Patients

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[19)] Participants were patients falling into "definite," "probable," or "probable-laboratory supported" ALS according to the El Escorial and Airlie House diagnostic criteria,[20)] who have a Japanese ALS severity classification of 1 or 2, a percent predicted forced vital capacity (%FVC) of ≥70%, and ALS disease duration of ≤3 years at the time of informed consent.

[20)] In the Escorial and Airlie House diagnostic criteria, the certainty of diagnosis is classified into the following 5 grades.

1. Clinically definite ALS: upper motor neuron (UMN) and lower motor neuron (LMN) signs in 3 regions.
2. Clinically probable ALS: UMN and LMN signs in at least 2 regions, with UMN signs rostral to LMN signs.
3. Clinically probable-laboratory-supported ALS: UMN and LMN signs in only 1 region or UMN signs in 1 region in addition to LMN signs detected by EMG criteria in at least 2 limbs, with proper application of neuroimaging or other clinical laboratory protocols to exclude other causes.
4. Clinically possible ALS: UMN and LMN signs in only 1 region or UMN signs alone in ≥2 regions; or LMN signs rostral to UMN signs. These signs do not fall under clinically probable-laboratory-supported ALS, but other diagnoses must have been excluded to accept a diagnosis of clinically possible ALS.
5. Clinically suspected ALS: a pure LMN syndrome, wherein the diagnosis of ALS could not be regarded as sufficiently certain to include the patient in a research study. Hence, this category is deleted from the revised El Escorial Criteria for the Diagnosis of ALS.

who completed this study were to be enrolled in an extension study (5.3.5.1-3, Study MCI186-17) or discontinue treatment.

All 206 randomized patients (104 and 102patients in the placebo and edaravone groups, respectively) were included in the safety analysis set. Of these, 205 patients (104 and 101 patients in the placebo and edaravone groups, respectively) were included in the FAS for efficacy analysis, and the remaining 1 patient with a disease other than ALS in the edaravone group was excluded. The study was discontinued in 23 patients (14 and 9 patients in the placebo and edaravone groups, respectively) mainly due to the patient's request in 10 patients (5 and 5 patients in the placebo and edaravone groups, respectively), occurrence of adverse events in 9 patients (6 and 3 patients in the placebo and edaravone groups, respectively), and tracheostomy in 3 patients (2 and 1 patients in the placebo and edaravone groups, respectively).

The primary endpoint was the ALS Functional Rating Scale-Revised (ALSFRS-R) score. The first primary analysis[21)] was made to compare the changes in the ALSFRS-R score from immediately before cycle 1 to 2 weeks after the final dose in cycle 6 or at the time of discontinuation of the study (LOCF)[22)] between the placebo and edaravone groups in the FAS. As Table 2 summarizes, no statistically significant difference between the 2 groups was observed. In the second primary analysis,[21)] a repeated-measures analysis of variance was used to analyze ALSFRS-R scores at each time point in the FAS.[23)] No significant interaction between group and time was observed ($P = 0.9151$), and the adjusted mean ALSFRS-R score (± standard error) was 37.43 ± 0.46 in the placebo group and 38.08 ± 0.47 in the edaravone group; the difference between the 2 groups [95% confidence interval] was 0.65 [-0.22, 1.52], with no statistically significant difference between the placebo and edaravone groups ($P = 0.1415$).

Table 2. Changes in ALSFRS-R score in Study MCI186-16 (FAS, LOCF)[a)]

Group	No. of patients evaluated	ALSFRS-R score[b)]		Change [c) d)]	Comparison with placebo[d)]	
		Before cycle 1 of treatment	At 2 weeks after the final dose in cycle 6 or at discontinuation		Difference between the groups [e)]	P value
Placebo group	99	41.1 ± 2.9	35.1 ± 7.4	-6.35 ± 0.84	0.65 [-0.90, 2.19]	0.4108
Edaravone group	100	40.5 ± 3.5	35.3 ± 7.1	-5.70 ± 0.85		

a) Patients who completed at least the first 3 cycles of treatment (i.e., day 81 of treatment) were assessed.
b) Mean ± standard deviation
c) Adjusted mean ± standard error
d) Based on an analysis of variance model using treatment group, the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4), initial symptoms (bulbar symptoms/limb symptoms), and the use of riluzole as factors.
e) Edaravone group minus placebo group [95% CI]

21) The protocol defined that the efficacy of edaravone was to be demonstrated when either of the 2 primary analyses revealed a significant difference between the placebo and Radicut groups. Multiplicity of the tests was not adjusted.

22) When the change in ALSFRS-R score was calculated, missing data at 2 weeks after the final dose in cycle 6 were replaced by the last observed value (the LOCF method). However, this method was to be applied only to patients who completed study treatment at least by the end of cycle 3 (i.e., day 81 of treatment). Accordingly, 6 patients (5 patients in the placebo group and 1 patient in the edaravone group) who did not complete the first 3 cycles of treatment were excluded from analysis.

23) Treatment group, time, interaction between treatment group and time, ALSFRS-R score immediately before cycle 1 treatment, the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4), initial symptoms (bulbar symptoms/limb symptoms), and use of riluzole were used as factors. The structure of the covariance matrix was set to compound symmetry.

Adverse events, including abnormal laboratory findings, were observed in 92 of 104 patients (88.5%) in the placebo group and 91 of 102 patients (89.2%) in the edaravone group. There were 2 deaths (respiratory failure in 2 patients) in the placebo group and 3 deaths (respiratory disorder in the 2 patients, and respiratory failure in 1 patient) in the edaravone group. The investigators concluded that the cases of death were due to the progression of ALS and ruled out a causal relationship between the death and the study drug.[16)] As Table 3 shows, serious adverse events other than death were observed in 23 patients in the placebo group and 17 patients in the edaravone group. A causal relationship between these events and the study drug was ruled out.[16)]

Table 3. Serious adverse events other than death in Study MCI186-16

Placebo group	Dysphagia in 7 patients; gait disturbance/vertigo positional/mastication disorder/musculoskeletal disorder/dysphagia, ascites/peripheral edema/hypoproteinaemia/gastric cancer, dysphagia/dyslalia/ pneumonia aspiration, dysphagia/respiratory failure, depression/musculoskeletal disorder, subdural hematoma/respiratory failure, aspiration/dysphagia, respiratory failure, dyslalia, anxiety, gait disturbance, haemoptysis, musculoskeletal disorder, cellulitis, muscular weakness, and muscle spasms in 1 patient each
Edaravone group	Dysphagia in 4 patients; dysphagia/sputum retention/gait disturbance/dyspnoea/musculoskeletal disorder, gait disturbance/muscular weakness/musculoskeletal disorder, abdominal pain/dysphagia, respiratory disorder/dysphagia, dyspnoea/dysphagia, pneumonia/abasia/intestinal ischaemia/ gastroenteritis/dyslalia/musculoskeletal disorder/respiratory disorder in 1 patient each.

Adverse events, including abnormal laboratory findings, for which a causal relationship to the study drug could not be ruled out[16)] were observed in 20 of 104 patients (19.2%) in the placebo group and 14 of 102 patients (13.7%) in the edaravone group. The most commonly observed adverse events included hepatic function abnormal in 5 patients (4 and 1 patients in the placebo and edaravone groups, respectively), glucose urine present in 3 patients (1 and 2 patients in the placebo and edaravone groups, respectively), constipation in 3 patients (2 and 1 patients in the placebo and edaravone groups, respectively), and white blood cell count decreased in 2 patients (2 and 0 patients in the placebo and edaravone groups, respectively).

No systematic evaluation of vital signs and electrocardiogram were made in the study.

On the basis of the above findings, the applicant explained that the efficacy of edaravone in patients with ALS did not be demonstrated in the study, but that there were no major problems in terms of safety.

3.(ii).A.(2).2) Confirmatory Study 2 (5.3.5.1-1, Study MCI186-19 [20 to 20])

A placebo-controlled, randomized, double-blind, parallel group comparison study was conducted in Japanese patients with ALS[24)] (target sample size: 128 patients in total; 64 patients each in the placebo and edaravone groups), to assess the efficacy and safety of edaravone.

During the double-blind phase, patients were to receive placebo or edaravone at a dose of 60 mg once

[24)] Participants were patients falling into "definite" or "probable" ALS according to the El Escorial and Airlie House diagnostic criteria[20)] and into grade 1 or 2 ALS according to the Japanese ALS severity classification, who have a %FVC of ≥80%, scores of ≥2 in all items of the ALSFRS-R criteria, and ALS disease duration of ≤2 years at the time of informed consent for the study.

daily by intravenous infusion over 60 minutes. The first cycle of treatment consisted of a 2-week daily treatment period followed by a 2-week rest period. In each of cycles 2 to 6 of treatment (i.e., a total of 5 cycles), a total of 10 doses of the study drug were administered during a 2-week treatment period followed by a 2-week rest period. Patients who had completed the double-blind phase and who had been willing to enter the open-label phase received an additional 6 cycles of treatment (cycles 7 to 12 of treatment). Each additional cycle consisted of a 2-week treatment period, during which a total of 10 doses of edaravone (60 mg once daily) were administered, followed by a 2-week rest period.

During the double-blind phase, all 137 randomized patients (68 and 69 patients in the placebo and edaravone groups, respectively) were included in the FAS for efficacy analysis and also included in the safety analysis set. Ten patients (8 and 2 patients in the placebo and edaravone groups, respectively) discontinued the study during the double-blind phase; the main reasons for discontinuation included the patient's request in 2 patients (2 and 0 patients in the placebo and edaravone groups, respectively), occurrence of adverse events in 2 patients (2 and 0 patients in the placebo and edaravone groups, respectively), tracheostomy in 2 patients (1 and 1 patient in the placebo and edaravone groups, respectively), deterioration of respiratory function in 2 patients[25] (1 and 1 patient in the placebo and edaravone groups, respectively).

During the open-label phase, all the 123 patients enrolled in the study (58 patients who were in the placebo group during the double-blind phase [PM subgroup], and 65 patients who were in the edaravone group during the double-blind phase [MM subgroup]) were included in the FAS for efficacy analysis and also included in the safety analysis set. A total of 30 patients (18 patients and 12 patients in the PM and MM subgroups, respectively) discontinued the study; the main reasons for discontinuation included the patient's request in 13 patients (7 and 6 patients in the PM and MM subgroups, respectively), deterioration of respiratory function[25] in 10 patients (6 and 4 patients in the PM and MM subgroups, respectively), and occurrence of adverse events in 3 patients (2 and 1 patients in the PM and MM subgroups, respectively).

Table 4 summarizes the results of the primary endpoint, the change in ALSFRS-R score in the FAS from immediately before cycle 1 to 2 weeks after the final dose in cycle 6 or at the time of discontinuation in the double-blind phase.[26),27] A statistically significant difference in change in ALSFRS-R score was observed between the placebo and edaravone groups.

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[25] Patients met one of criteria for discontinuation, i.e., "a %FVC of ≤50% and a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of ≥45 mmHg."

[26] When the change in ALSFRS-R score was calculated, missing data at 2 weeks after the final dose in cycle 6 were replaced by the last observed value (the LOCF method). However, this method was to be applied only to patients who completed study treatment at least by the end of cycle 3 (i.e., day 81 of treatment). Accordingly, 3 patients (2 patients in the placebo group and 1 patient in the edaravone group) who did not complete the first 3 cycles of treatment were excluded from analysis.

[27] ALSFRS-R data during cycle 2 of treatment in 1 patient in the edaravone group were excluded from analysis because the data were obtained by an investigator who had not attended ALSFRS-R training.

Table 4. Change in ALSFRS-R score in the double-blind phase of the Study MCI186-19 (double-blind phase, FAS, LOCF)[a)]

Treatment group	No. of patients evaluated	ALSFRS-R score[b)]		Change [c) d)]	Comparison with placebo[d)]	
		Before cycle 1 of treatment	At 2 weeks after the final dose in cycle 6 or at discontinuation		Difference between the groups[e)]	P value
Placebo group	66	41.9 ± 2.2	35.0 ± 5.6	-7.50 ± 0.66	2.49 [0.99, 3.98]	0.0013
Edaravone group	68	41.9 ± 2.5	37.5 ± 5.3	-5.01 ± 0.64		

a) Patients who completed at least the first 3 cycles of treatment (i.e., day 81 of treatment) were assessed.

b) Mean ± standard deviation

c) Adjusted mean ± standard error

d) Based on an analysis of variance model using treatment group, the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4), diagnosis based on El Escorial and Airlie House diagnostic criteria (definite/probable), and age (≥ 65 years/< 65 years) as factors.

e) Edaravone group minus placebo group [95% CI]

Table 5 summarizes changes in ALSFRS-R score during the open-label study phase.

Table 5. Change in ALSFRS-R score in the open-label phase of the Study MCI186-19 (open-label phase, observed case [OC])[a)]

Treatment population	Before cycle 1 of treatment	Before cycle 7 of treatment	At 2 weeks after the final dose in cycle 12	Change from immediately before cycle 1 to 2 weeks after the final dose in cycle 12
PM subgroup	41.7 ± 2.2 (58)	34.8 ± 5.8 (58)	30.8 ± 7.7 (37)	-10.9 ± 6.9 (37)
MM subgroup	41.9 ± 2.5 (65)	37.8 ± 4.9 (65)	34.1 ± 7.2 (51)	-8.0 ± 5.6 (51)

Mean ± standard deviation (No. of patients assessed)

Adverse events, including abnormal laboratory findings, were observed in 57 of 68 patients (83.8%) in the placebo group and 58 of 69 patients (84.1%) in the edaravone group during the double-blind phase, and in 48 of 58 patients (82.8%) in the PM subgroup and 53 of 65 patients (81.5%) in the MM subgroup during the open-label phase. No patients died during the double-blind phase. During the open-label phase, there were 4 deaths (stress cardiomyopathy/respiratory failure, pneumonia aspiration/respiratory failure, pneumonia aspiration, and respiratory disorder [1 patient each]) in the PM subgroup and 2 deaths (respiratory disorder and respiratory failure [1 patient each]) in the MM subgroup. A causal relationship between these events and the study drug was ruled out.[28)] As Table 6 shows, serious adverse events other than death occurred in 16 patients in the placebo group and 11 patients in the edaravone group during the double-blind phase; and 20 patients in the PM subgroup and 16 patients in the MM subgroup during the open-label phase. A causal relationship between these events and the study drug was ruled out.[28)]

[28)] A causal relationship between the event and the study drug was assessed in terms of whether there is "a reasonable possibility" that the drug caused the event. Adverse events "with a reasonable possibility" were classified into adverse events for which a causal relationship cannot be ruled out, and those "without a reasonable possibility" into adverse events for which a causal relationship can be ruled out.

Table 6. Serious adverse events other than death in Study MCI186-19

Double-blind phase	Placebo group	Dysphagia in 5 patients; pneumonia aspiration/drug-induced liver injury/dysphagia, dysphagia/pneumonia aspiration, respiratory disorder/speech disorder, dysphagia/ depression, dyspnoea, musculoskeletal disorder, speech disorder, lower gastrointestinal haemorrhage, contusion, respiratory disorder, and bacterial infection in 1 patient each
	Edaravone group	Dysphagia in 7 patients; respiratory disorder in 2 patients; dysphagia, speech disorder, and bacterial infection in 1 patient each
Open-label phase	PM subgroup	Dysphagia in 9 patients; respiratory disorder in 2 patients; dyspnoea/dysphagia, lower gastrointestinal haemorrhage/dysphagia, dysphagia/respiratory disorder, pneumonia aspiration/musculoskeletal disorder, dysphagia/depression, respiratory failure, contusion, speech disorder, and musculoskeletal disorder in 1 patient each
	MM subgroup	Dysphagia in 4 patients; dysphagia/musculoskeletal disorder/speech disorder, musculoskeletal disorder/gait disturbance, respiratory disorder/pneumonia aspiration, bronchitis/pneumonia aspiration, dyspnoea/dysphagia, respiratory disorder/shock, musculoskeletal disorder, speech disorder, cholecystitis, gait disturbance, respiratory disorder, and adjustment disorder in 1 patient each

Adverse events, including abnormal laboratory findings, for which a causal relationship to the study drug could not be ruled out[28] were observed in 5 of 68 patients (7.4%) in the placebo group and 2 of 69 patients (2.9%) in the edaravone group during the double-blind phase; and 3 of 58 patients (5.2%) in the PM subgroup and 4 of 65 patients (6.2%) in the MM subgroup during the open-label phase. Among those, liver function test abnormal observed in 2 patients (1 each in the placebo and edaravone groups) was the most common adverse event during the double-blind phase, and there were no adverse events that developed in ≥2 patients during the open-label phase.

No systematic evaluation of vital signs and electrocardiogram were made in the study.

On the basis of the above, the applicant explained that the efficacy of edaravone in patients with ALS was demonstrated, and that there were no major problems in terms of safety.

3.(ii).A.(3) Extension study (5.3.5.1-3, Study MCI186-17 [20 to May 2009)

A placebo-controlled, randomized, double-blind, parallel comparison study was conducted in patients who had completed the confirmatory study 1 (5.3.5.1-2, Study MCI186-16) (target sample size: 105 patients in the edaravone group and 35 patients in the placebo group) to assess persistence of the efficacy of edaravone as well as the efficacy and safety of long-term treatment with edaravone. Patients consisted of 3 groups: those who had received edaravone in the confirmatory study 1 and placebo in the extension study (MP group), those who had received edaravone in both studies (MM group), and those who had received placebo in the confirmatory study 1 and edaravone in the extension study (PM group).[29]

Patients were to receive placebo or edaravone at a dose of 60 mg once daily by intravenous infusion of over 60 minutes. In each of cycles 7 to 12 of treatment (i.e., a total of 6 cycles),[30] a total of 10 doses of the study drug were administered during a 2-week treatment period followed by a 2-week rest period.

[29] Patients were randomly assigned to these 3 groups at the time of randomization prior to the confirmatory study 1.

[30] The number of cycles is counted from the beginning of the treatment in the confirmatory study 1 (5.3.5.1-2, Study MCI186-16).

During the period of additional 3 cycles (from cycles 13 to 15 of treatment), all patients received edaravone at the same dosage regimens.[30)]

All 181 randomized patients (45 patients in the MP group, 48 patients in the MM group, and 88 patients in the PM group) were analyzed for safety. After excluding 1 patient with a disease other than ALS in the MP group, 180 patients (44 patients in the MP group, 48 patients in the MM group, and 88 patients in the PM group) were included in the FAS for efficacy analysis. A total of 37 patients (7 patients in the MP group, 14 patients in the MM group, and 16 patients in the PM group) discontinued the study; the main reasons for discontinuation were tracheostomy in 14 patients (1 patient in the MP group, 7 patients in the MM group, and 6 patients in the PM group), the patient's request in 11 patients (4 patients in the MP group, 2 patients in the MM group, and 5 patients in the PM group), and occurrence of adverse events in 7 patients (2 patients in the MP group, 3 patients in the MM group, and 2 patients in the PM group).

Table 7 summarizes the efficacy endpoint of the study, i.e., the change in ALSFRS-R score from immediately before cycle 7 to 2 weeks after the final dose in cycle 12 or at the time of discontinuation (LOCF) in the FAS.[31)]

Table 7. Changes in ALSFRS-R score in Study MCI186-17 (FAS, LOCF)[a)]

Treatment group	No. of patients evaluated	ALSFRS-R score[b)]		Change[c) d)]	Comparison with MP group[d)]	
		Immediately before cycle 7	At 2 weeks after the final dose in cycle 12 or at discontinuation (LOCF)		Difference between the groups [e)]	P value
MP group	41	36.8 ± 5.5	31.5 ± 7.7	-5.51 ± 0.73		
MM group	44	36.5 ± 5.6	32.3 ± 8.2	-4.37 ± 0.69	1.15 [-0.76, 3.06]	0.2378
PM group	80	36.4 ± 6.5	30.8 ± 9.1	-5.76 ± 0.53		

a) Patients who completed at least the first 9 cycles of treatment (i.e., day 249 of treatment) were assessed.
b) Mean ± standard deviation
c) Adjusted mean ± standard error
d) Based on an analysis of variance model using treatment group and the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4) as factors.
e) MM group minus MP group [95% CI]

Adverse events, including abnormal laboratory findings, were observed in 44 of 45 patients (97.8%) in the MP group, 44 of 48 patients (91.7%) in the MM group, and 81 of 88 patients (92.0%) in the PM group. Death occurred in 2 patients in the MP group (respiratory failure in 2 patients), 4 patients in the MM group (respiratory failure in 2 patients, and bronchopneumonia, and respiratory failure/pneumonia in 1 patient each), and 1 patient in the PM group (cardiac arrest). All cases of death other than 1 in the PM group (cardiac arrest) were considered to be related with the progression of ALS. For all cases of death, including the death due to cardiac arrest, a causal relationship between the event and the study drug was ruled out.[16)] As Table 8 shows, serious adverse events other than death were observed in 13

[31)] When the change in ALSFRS-R score was calculated, missing data at 2 weeks after the final dose in cycle 12 were replaced by the last observed value (the LOCF method). However, this method was to be applied only to patients who completed study treatment at least by the end of cycle 9 (i.e., day 249 of treatment). Accordingly, 15 patients (3 patients in the MP group, 4 patients in the MM group, and 8 patients in the PM group) who did not complete the first 9 cycles of treatment were excluded from analysis. Data obtained within 339 days after the first dose in the first cycle were used as data at the discontinuation of the study.

patients in the MP group, 22 patients in the MM group, and 39 patients the PM group. A causal relationship between these events and the study drug was ruled out.[16)]

Table 8. Serious adverse events other than death in Study MCI186-17

MP group	Dysphagia in 3 patients; musculoskeletal disorder in 2 patients; dyslalia/bronchitis/dysphagia/sputum retention, musculoskeletal disorder/enterocolitis/pneumonia aspiration/ dyspnoea, musculoskeletal disorder/dysarthria, prostate cancer/dysphagia, dysphagia/respiratory disorder, diverticulitis, dyspnoea, and humerus fracture in 1 patient each.
MM group	Dysphagia in 6 patients; dyspnoea in 3 patients; respiratory failure, gait disturbance, and musculoskeletal disorder in 2 patients each; abasia/bronchitis/respiratory failure/dysphagia, musculoskeletal disorder/ respiratory disorder/dysphagia/stomach discomfort, dysphagia/respiratory disorder/gait disturbance, gait disturbance/musculoskeletal disorder, muscular weakness/musculoskeletal disorder, musculoskeletal disorder/bladder cancer, and pneumonia aspiration in 1 patient each.
PM group	Dysphagia in 7 patients; musculoskeletal disorder in 4 patients; muscular weakness, gait disturbance, and respiratory failure in 2 patients each; musculoskeletal disorder/dysphagia/respiratory failure/dyslalia/gait disturbance, musculoskeletal disorder/respiratory disorder/dyslalia/gait disturbance/dysphagia, dyslalia/dysphagia/muscular weakness/respiratory failure, dysphagia/abasia/herpes zoster/ musculoskeletal disorder, respiratory failure/respiratory arrest/musculoskeletal disorder/dysphagia, musculoskeletal disorder/dysphagia/catheter site infection/pneumonia, dysphagia/dyslalia/dyspnoea, dysphagia/hypercapnia/respiratory failure, head injury/skin tear/dysphagia, dysphagia/respiratory disorder, dysphagia/dyslalia, musculoskeletal disorder/dysphagia, pneumonia/dysphagia, dysphagia/gait disturbance, dysphagia/sputum retention, retinal vein occlusion, pneumonia aspiration, colonic polyp, joint sprain, gastric ulcer, dyspnoea, and dyslalia in 1 patient each.

Adverse events, including abnormal laboratory findings, for which a causal relationship with the study drug cannot be ruled out,[16)] were observed in 2 patients in the MP group, 5 patients in the MM group, and 9 patients in the PM group. The major adverse events included rash in 4 patients (1, 1, and 2 patients in the MP, MM, and PM groups, respectively), liver disorder in 3 patients (0, 0, and 3 patients in the MP, MM, and PM groups, respectively), and hypertension in 2 patients (0, 2, and 0 patients in the MP, MM, and PM groups, respectively).

No systematic evaluation of vital signs and electrocardiogram were made in the study.

On the basis of the above findings, the applicant explained as follows:
It was difficult to assess the long-term efficacy of edaravone in this study because the efficacy of treatment with edaravone could not be demonstrated in the confirmatory study 1. Since serious adverse events developed more commonly in the MM group than in the MP group, it should be noted that physicians should carefully consider the risk-benefit profile of edaravone before starting long-term use of this drug in patients with ALS.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Clinical positioning

PMDA asked the applicant to explain the clinical positioning of edaravone in the treatment of ALS.

The applicant explained as follows:
Currently no curative threapy is available for ALS, and riluzole, an oral agent, is the only drug currently recommended and used for the treatment of ALS in Japan and other countries. Dysphagia and respiratory disorders associated with the progression of ALS are treated only symptomatically (the Japanese Society

of Neurology, *Practical Guidelines for Amyotrophic Lateral Sclerosis 2013*;2013). It has been reported that riluzole may prolong the time to death or intubation/tracheostomy for mechanical ventilation by an average of 2 to 3 months (the Japanese Society of Neurology, *Practical Guidelines for Amyotrophic Lateral Sclerosis 2013*;2013). However, Japanese phase III clinical studies of riluzole did not demonstrate the superiority of riluzole over placebo in terms of the time to death or a specific stage of disease, which was evaluated as the primary endpoint, and therefore the package insert for riluzole includes precautions stating that the physician should inform the patient of the results of these clinical studies and should obtain informed consent from him/her before using the drug. The confirmatory study 2 (5.3.5.1-1, Study MCI186-19) demonstrated the superiority of edaravone over placebo in terms of slowing of progression of ALS-associated functional impairement, although the following matters should be noted: (1) the number of ALS patients is limited; and (2) the primary endpoint was not the time to death or a certain stage of disease but the change in ALSFRS-R score. Also, riluzole is considered to exert its protective action on motor neurons in patients with ALS by inhibiting the release of excitatory amino acid from the presynaptic terminals and inhibiting the persistent sodium current (Bellingham MC, *CNS Neurosci Ther*. 2011;17:4-31). Taking into account the fact that edaravone has a mechanism of action different from riluzole, the applicant considers that edaravone can provide an important option for the treatment of ALS.

PMDA considered as follows:
On the basis of the facts that ALS is a serious and fatal disease, and that currently there are no drugs which has been demonstrated to be effective in Japanese patients with ALS, the results of the confirmatory study in which edaravone was demonstrated to be effective in slowing down the progression of functional impairment in ALS patients [see "3.(ii).B.(2).1) Efficacy of edaravone in the confirmatory study 2"] are significant. Edaravone can therefore be expected to provide a new option for the treatment of ALS.

3.(ii).B.(2) Efficacy of edaravone

3.(ii).B.(2).1) Efficacy of edaravone in the confirmatory study 2

PMDA asked the applicant to explain the appropriateness of using ALSFRS-R score as the primary endpoint in the confirmatory study 2 (5.3.5.1-1, Study MCI186-19) and the clinical significance of the study results.

The applicant explained as follows:
A long-term, placebo-controlled study of >6 months is not feasible because edaravone is a drug for intravenous infusion which would place a larger burden on patients than oral drugs, and because patients need to visit or stay in a hospital to receive edaravone. Therefore, ALSFRS-R, a measure of functional impairement, rather than the time to death or a certain stage of disease, was used as the primary endpoint in the confirmatory studies including Study MCI186-19. ALSFRS-R is an ALS severity scale used worldwide in clinical studies in ALS patients (the Japanese Society of Neurology, *Practical Guidelines*

for Amyotrophic Lateral Sclerosis 2013;2013), and has been used as the primary endpoint in clinical studies of several drugs in many countries.[32)] In a study in 267 patients with ALS conducted to prospectively assess the relationship between the ALSFRS-R score at the first visit and the occurrence of death or tracheostomy during a mean follow-up of 1 year, the ALSFRS-R score at baseline may be a predictor of death or tracheostomy.[33)] In Japan, the Japanese version of ALSFRS-R was developed by modifying the original version to reflect the lifestyle of Japanese patients. The Japanese version ALSFRS-R was validated for inter- and intra-rater reliability and also assessed for the correlation between the change in ALSFRS-R score and the change in the Global Clinical Impression of Change score evaluated subjectively by neurologists in specific periods of time in 30 Japanese ALS patients in 5 institutions. The results indicated that both the global total score and itemized scores of ALSFRS-R are reliable and may be used in clinical assessment of ALS (Ohashi Y, et al., *Advances in Neurological Sciences*. 2001;53:346-355)

The applicant explained that the slowing of progression of functional impairment observed in ALS patients receiving edaravone in Study MCI186-19 was clinically relevant for the following reasons:

- As Figure 1 shows, the ALSFRS-R scores decreased nearly linearly with time both in the placebo and edaravone groups in Study MCI186-19. The mean ALSFRS-R score at 2 weeks after cycle 6 of treatment in the edaravone group (37.5) was similar to that at 2 weeks after cycle 4 of treatment in the placebo group (37.8). The period to reach this stage of disease was 6 months in the edaravone group and 4 months in the placebo group, indicating that 6 cycles of edaravone treatment may slow down the progression of functional impairment by approximately 2 months.

[32)] Cudkowicz M et al., *Nat Med*. 2011;17:1652-1656, Meininger V, et al., *Amyotroph Lateral Scler*. 2009;10: 378-383, Kaufmann P, et al., *Ann Neurol*. 2009;66:235-244, Gordon PH. *Lancet Neurol*. 2007;6:1045-1053, Miller R, et al., *Neurology*. 2007;69:776-784

[33)] An analysis with Cox proportional hazards models using age at the first visit, sex, disease duration, ALSFRS-R score, %FVC, history of riluzole therapy, and initial symptoms (upper limb symptoms/lower limb symptoms/bulbar symptoms/respiratory symptoms) as covariates revealed that baseline ALSFRS-R score was associated with death or tracheostomy with a hazard ratio of 0.93 [95% CI, 0.90-0.96] during the mean follow-up of 1 year (Kaufmann P, et al., *Neurology*. 2005;64:38-43).

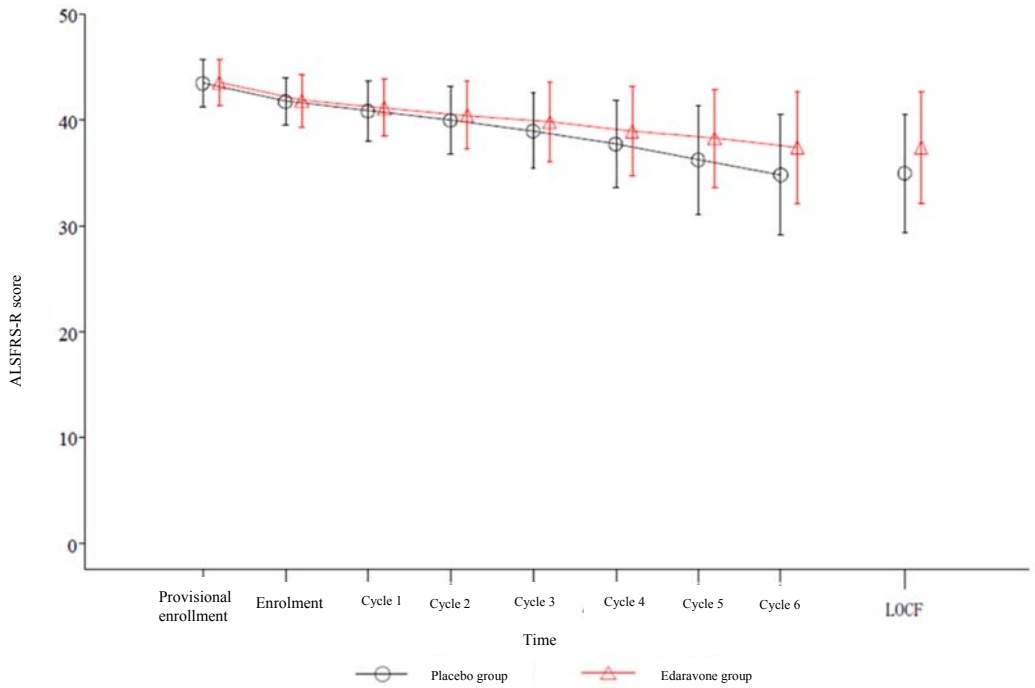

Figure 1. Change in ALSFRS-R score (Mean ± standard deviation) in Study MCI186-19 (FAS)

- Study MCI186-19 was not designed to adequately evaluate the occurrence of events such as death and tracheostomy. Since specific respiratory conditions were included in the criteria for study discontinuation, 6 patients in the placebo group and 4 patients in the edaravone group discontinued the study before undergoing tracheostomy, and the number of occurrence of pre-specified events related to the progression of ALS was limited in Study MCI186-19: Loss of independent walking[34] (2 and 0 patients in the placebo and edaravone groups, respectively), loss of upper limb function[35] (0 and 0 patients in the placebo and edaravone groups, respectively), tracheostomy (0 and 1 patients in the placebo and edaravone groups, respectively), introduction of mechanical ventilation (0 and 0 patients in the placebo and edaravone groups, respectively), tube feeding[36] (1 and 0 patients in the placebo and edaravone groups, respectively), and loss of useful speech[37] (3 and 1 patients in the placebo and edaravone groups, respectively). Accordingly, no statistically significant differences in the number of or time to events related to disease progression were observed between the edaravone and placebo groups. However, when a decline in "forced vital capacity (%FVC) to <50%," which is "a criterion for assessment of ALS patients requiring respiratory support" (the Japanese Society of Neurology, *Practical Guidelines for Amyotrophic Lateral Sclerosis 2013*, 2013), was defined as a respiratory-related event, the incidence of respiratory-related events during the evaluation period was 11.8% (8 of 68 patients) in the placebo group and 2.9% (2 of 69 patients) in the edaravone group.

[34] Loss of walking was defined as ALSFRS-R Q8 walking score of 0 (no purposeful leg movement).

[35] Loss of upper limb function was defined as every ALSFRS-R Q4 handwriting score, Q5 cutting food score, and Q6 dressing and hygiene score of 0. (Specifically, a handwriting score of 0 is described as "unable to grip pen;" a cutting food score of 0 is described as "need to be fed" for patients without gastrostomy and "unable to perform any aspect of task" for patients with gastrostomy in term of handling utensils; and a dressing and hygiene score of 0 is described as "total dependence.")

[36] Tube feeding was defined as Q3 swallowing score of 0 "exclusively parenteral or enteral feeding."

[37] Loss of useful speech was defined as Q1 speech score of 0 "loss of useful speech."

Although the number of the events was small, the time to event differed significantly between the placebo and edaravone groups ($P = 0.0459$, log-rank test), suggesting that edaravone may slow down the decline in respiratory function.

- Table 9 outlines changes over time in other major secondary endpoints in Study MCI186-19. Statistically significant differences were observed in physical function scores evaluated with the Modified Norris Scale[38] and QOL scores with the 40-item ALS assessment questionnaire (ALSAQ-40)[39] between the edaravone and placebo groups. Respiratory function evaluated with %FVC did not differ statistically significantly between the placebo and edaravone groups, but the decline in respiratory function tended to be slower in the edaravone group than in the placebo group. These findings indicate a consistent effect of edaravone to slow down the progression of ALS.

Table 9. Changes in Modified Norris Scale, %FVC, and ALSAQ40 score in Study MCI186-19 (FAS, LOCF)[a]

Scale	Treatment group	No. of patients evaluated	Summary statistics [b]		Change [c) d)]	Comparison with placebo [d]	
			Before cycle 1 of treatment	At 2 weeks after the final dose in cycle 6 or at discontinuation		Difference between the groups [e]	P value
Modified Norris Scale	Placebo group	63	88.1 ± 6.6	70.5 ± 16.7	-20.80 ± 2.06		
	Edaravone group	68	88.1 ± 7.7	75.2 ± 15.4	-15.91 ± 1.97	4.89 [0.24, 9.54]	0.0393
%FVC	Placebo group	66	97.7 ± 13.6	80.5 ± 24.0	-20.40 ± 2.48		
	Edaravone group	67	100.8 ± 14.9	88.0 ± 23.9	-15.61 ± 2.41	4.78 [-0.83, 10.40]	0.0942
ALSAQ40	Placebo group	64	91.5 ± 19.8	117.2 ± 26.7	26.04 ± 3.53		
	Edaravone group	68	88.8 ±21.2	105.7 ± 26.2	17.25 ± 3.39	-8.79 [-16.76, -0.82]	0.0309

a) Data from patients who completed at least the first 3 cycles of treatment (i.e., Day 81 of treatment) were analyzed for each item.
b) Mean ± standard deviation
c) Adjusted mean ± standard error
d) Based on an analysis of variance model using treatment group, the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4), diagnosis based on the El Escorial and Airlie House diagnostic criteria (definite/probable), and age (≥ 65 years/< 65 years) as factors.
e) Edaravone group minus placebo group [95% CI]

PMDA considers as follows:

Since death or tracheostomy or the introduction of mechanical ventilation for the treatment of respiratory failure are clinically relevant events in patients with ALS, confirmatory studies should verify the effects of edaravone to reduce the occurrence of these events representing the progression of ALS. However, the number of ALS patients in Japan is extremely limited, and thus it is difficult to conduct a clinical study large enough to accumulate a sufficient number of events in a specific period of time. Also, given that edaravone must be administered once daily by intravenous infusion for a total of 10 doses during a 2-week treatment period followed by a 2-week rest period and that clinical studies of edaravone involve long-term hospital visit or stay, the conduct of such a study in the intended patient population is

[38] The Modified Norris Scale is a rating scale for ALS, which consists of the Limb Norris Scale (21 items) and the Norris Bulbar Scale (13 items). Each item is rated on a 4-point scale (0-3). The higher score represents better condition.

[39] ALSAQ40 is a disease-specific quality of life (QOL) grading scale for ALS patients, and consists of 40 questions in 10 categories, such as problems with walking, upper limb function, swallowing, eating, and communication as well as emotional functioning (e.g., felt lonely, felt hopeless, felt depressed, felt anxious about the future). The lower score represents better condition.

considered difficult. Thus, it is understandable that the occurrence of events was not investigated as the primary endpoint. Meanwhile, ALSFRS-R, evaluated as the primary endpoint in Study MCI186-19, has been globally used as a measure of functional impairment in ALS patients, and findings have demonstrated that edaravone slows down the progression of functional impairement on the basis of changes in ALSFRS-R score over time. Edaravone also slowed down the progression of ALS as compared with placebo in terms of physical function evaluated with the Modified Norris Scale, QOL evaluated with ALSAQ40, respiratory function evaluated with %FVC, and the occurrence of respiratory events. These findings indicate the efficacy of edaravone in slowing down the progression of functional impairement in ALS patients.

Since Study MCI186-19 was conducted in the limited patient population, due consideration should be given to determining eligible patients who are expected to respond to edaravone [see "3.(ii).B.(3) Intended patient population"]. It cannot be determined that edaravone may exert favorable effects to reduce the occurrence of events associated with disease progression, such as death and tracheostomy, on the basis of the results of evaluation using ALSFRS-R. Thus, post-marketing surveillance should be conducted to continue the investigation on the effect of edaravone on events associated with disease progression.

3.(ii).B.(2).2) Factors that may affect the efficacy of edaravone

PMDA asked the applicant to explain whether or not there are factors that may affect the efficacy of edaravone.

The applicant answered as follows:

As Table 10 shows changes in ALSFRS-R score by patient characteristics in the confirmatory study 2 (5.3.5.1-1, Study MCI186-19), in all subgroups other than patients with familial ALS, which were small in number, the change in ALSFRS-R score was smaller in ALS patients receiving edaravone than in those receiving placebo. In addition, the difference between the edaravone and placebo groups tended to be smaller in patients receiving concomitant treatment such as physical therapy, occupational therapy, and speech therapy than in those not receiving such. It cannot be ruled out that concomitant therapy may have contributed to the slowing of disease progression. However, most patients enrolled in Study MCI186-19 (59 of 66 patients [89.4%] in the placebo group and 58 of 68 patients [85.3%] in the edaravone group) received concomitant therapy during the study; there is a limit to assess the efficacy of edaravone with and without concomitant therapy. Analysis of differences between the groups by patient characteristics did not reveal any factors that may significantly affect the efficacy of edaravone.

Table10. Changes in ALSFRS-R score by patient characteristics in Study MCI186-19 (FAS, LOCF)[a)]

		Placebo group			Edaravone group			Difference between the groups [e)]
		No. of patients evaluated	Before cycle 1 of treatment[b)]	Change [c) d)]	No. of patients evaluated	Before cycle 1 of treatment[b)]	Change [c) d)]	
Sex	Male	39	41.8 ± 2.4	-7.32 ± 0.99	38	41.9 ± 2.9	-4.78 ± 0.93	2.54 [0.42, 4.66]
	Female	27	42.0 ± 1.8	-7.60 ± 0.90	30	41.8 ± 1.9	-5.24 ±0.91	2.36 [0.14, 4.58]
Age	<65 years	44	42.0 ± 2.3	-7.52 ± 0.86	46	42.2 ± 2.6	-5.21 ± 0.84	2.31 [0.33, 4.30]
	≥65 years	22	41.5 ± 2.0	-7.54 ± 0.96	22	41.2 ± 2.0	-4.80 ± 0.92	2.73 [0.46, 5.01]
Body weight[f)]	<56.0 kg	31	41.7 ± 2.0	-7.69 ± 0.91	34	41.7 ± 2.2	-4.48 ± 0.99	3.21 [0.90, 5.51]
	≥56.0 kg	35	42.0 ± 2.3	-7.31 ± 1.02	34	42.1 ± 2.7	-5.26 ± 0.88	2.05 [-0.08, 4.18]
Duration of disease	<1 year	32	42.2 ± 2.0	-7.92 ± 0.97	27	42.8 ± 2.4	-5.36 ± 1.05	2.56 [0.22, 4.90]
	≥1 year	34	41.6 ± 2.4	-6.74 ± 1.00	41	41.2 ± 2.4	-4.52 ± 0.89	2.22 [0.17, 4.28]
Initial symptoms	Bulbar symptoms	14	42.6 ± 1.9	-7.40 ± 1.16	15	41.5 ± 2.2	-4.98 ± 1.06	2.42 [-0.60, 5.43]
	Limb symptoms	52	41.7 ± 2.2	-7.53 ± 0.81	53	42.0 ± 2.5	-5.09 ± 0.81	2.44 [0.68, 4.21]
Revised El Escorial criteria	Definite	26	41.7 ± 2.1	-8.16 ± 1.07	28	41.6 ± 2.4	-6.02 ± 0.99	2.13 [-0.25, 4.51]
	Probable	40	42.0 ± 2.3	-7.14 ± 0.83	40	42.1 ± 2.5	-4.29 ± 0.85	2.85 [0.88, 4.82]
Type of ALS	Sporadic ALS	64	41.8 ± 2.1	-7.43 ± 0.66	67	41.9 ± 2.5	-5.02 ± 0.64	2.41 [0.90, 3.92]
	Familial ALS	2	40, 47[g)]	-13, -2[g)]	1	43[g)]	-1[g)]	-
ALS severity classification	Grade 1	16	43.3 ± 2.7	-5.81 ± 0.88	22	43.5 ± 1.7	-3.29 ± 0.84	2.51 [0.48, 4.55]
	Grade 2	50	41.4 ± 1.8	-7.99 ± 0.81	46	41.1 ± 2.4	-5.86 ± 0.79	2.14 [0.28, 3.99]
ALSFRS-R score[f)]	<42.0	27	39.7 ± 1.1	-7.74 ± 1.07	27	39.3 ± 14	-6.37 ± 0.96	1.38 [-1.30, 4.05]
	≥42.0	39	43.4 ± 1.4	-7.08 ± 0.84	41	43.5 ± 1.3	-4.10 ± 0.90	2.98 [1.24, 4.72]
Concomitant use of riluzole	Present	61	42.0 ± 2.2	-7.53 ± 0.70	62	41.9 ±2.4	-5.14 ± 0.68	2.39 [0.78, 3.99]
	Absent	5	40.8 ± 1.3	-5.34 ± 1.99	6	42.0 ± 3.2	-3.38 ± 1.94	1.96 [-3.45, 7.36]
Concomitant therapy	Present	59	41.8 ± 2.2	-7.12 ± 0.70	58	41.7 ± 2.4	-5.24 ± 0.69	1.88 [0.27, 3.49]
	Absent	7	42.3 ± 2.0	-10.86 ± 1.56	10	43.1 ± 2.6	-3.39 ± 1.46	7.48 [3.68, 11.28]

- : Not computable
a) Patients who completed at least the first 3 cycles of treatment (i.e., day 81 of treatment) were assessed.
b) ALSFRS-R score (mean ± standard deviation)
c) Change from immediately before cycle 1 to 2 weeks after the final dose in cycle 6 or at study discontinuation (LOCF)
d) Adjusted mean ± standard error
Based on an analysis of variance model using treatment group, the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4), diagnosis based on El Escorial and Airlie House diagnostic criteria (definite/probable), and age (≥65 years/<65 years) as factors (When patients were stratified by a factor for adjustment, a model not including the factor was used).
e) Edaravone group minus placebo group [95% CI]
f) Patients were categorized on the basis of the median of all participants immediately before cycle 1 of treatment.
g) Individual data

The applicant explained about the efficacy of edaravone in patients with familial ALS as follows:

Patients with familial ALS account for 5.1% of all ALS patients (the Japanese Society of Neurology, *Practical Guidelines for Amyotrophic Lateral Sclerosis 2013*;2013). Genetic mutations, known as the cause of familial ALS, is also detected in some patients with sporadic ALS. Symptoms of familial ALS are similar to those of sporadic ALS, which may make it difficult to distinguish one type of ALS from the other clinically or pathologically (Parakh S, et al., *Oxid Med Cell Longev*. 2013; 2013:Article ID 408681, Robberecht W, et al., *Nat Rev Neurosci*. 2013;14:248-264). As an increase in 3-nitrotyrosine in the cerebrospinal fluid is observed in both patients with familial ALS and those with sporadic ALS, free radical-induced oxidative stress is likely to partly contribute to the onset and progression of ALS (Parakh S, et al, *Oxid Med Cell Longev*. 2013; 2013:Article ID 408681). Edaravone may inhibit the degeneration and loss of neurons in ALS patients by reducing the generaion of oxidative stress. On the basis of these assumptions, edaravone is expected to be effective in both patients with familial ALS and those with sporadic ALS.

PMDA considers as follows:

The results of the clinical study etc., presented by the applicant revealed no factors that would substantially affect the efficacy of edaravone. However, due to the limited number of patients evaluated in each subgroup in the clinical studies, data collection should be continued in post-marketing surveillance to investigate whether or not patient characteristics such as the use of concomitant therapy and disease type (familial or sporadic ALS) affect the efficacy of edaravone.

3.(ii).B.(3) Intended patient population

In the confirmatory study 2 (5.3.5.1-1, Study MCI186-19) demonstrating the efficacy of edaravone in ALS patients, study subjects were limited according to specific disease conditions etc., at the time of enrollment. PMDA asked the applicant to justify the inclusion criteria and explain the clinical significance of the use of edaravone in patients not included in Study MCI186-19.

The applicant provided a comparison of major inclusion and exclusion criteria in pivotal clinical studies of edaravone (Table 11) and explained as follows:

In the confirmatory study 1 (5.3.5.1-2, Study MCI186-16) that enrolled ALS patients with more extensive eligibility criteria as compared with those used in Study MCI186-19, the superiority of edaravone over placebo could not be demonstrated. An additional analysis of the data from Study MCI186-16 (Tables 12 to 14, and Table 16) showed that the difference between the edaravone and placebo groups tended to be larger in patients "with 'definite' or 'probable' ALS assessed according to the El Escorial and Airlie House diagnostic criteria," those with "grade 1 or 2 ALS according to the Japanese ALS severity classification," those with "scores of ≥2 in all items of the ALSFRS-R," those with "a disease duration of ≤2 years," and those with "a %FVC of ≥80%." Since survival outcome and the progression of functional impairement may relatively vary among patients with ALS, the applicant developed the inclusion and exclusion criteria (Table 11) for Study MCI186-19 to enroll a homogenous patient population that may verify the efficacy of edaravone in slowing down the progression of functional impairement in ALS patients during a 6-month evaluation period. The criteria were modified to specify the patients with "scores of ≥2 in all items of the ALSFRS-R" in order not to enrol patients with disease conditions similar to those falling under the Japanese ALS severity classification grade 3.[40)]

[40)] The Japanese ALS severity classification grade 3 is defined as a "condition in which assistance is required for daily living, and unable to do at least one of eating, excretion, and ambulation, independently" which is considered to be equivalent to a score 1 (needs assistance) or 0 (total independence) in all items of the ALSFRS-R.

Table 11. Major inclusion and exclusion criteria in major clinical studies of edaravone

	Study MCI186-19	Study MCI186-16	MCI186-18 Study	Study MCI186-12
El Escorial and Airlie House diagnostic criteria	Definite or Probable	Definite, Probable, or Probable-laboratory-supported	Definite, Probable, or Probable-laboratory-supported	None
Japanese ALS severity classification	Grade 1 or 2	Grade 1 or 2	Grade 3	
ALSFRS-R score	Scores of ≥2 in all items	None	None	
Years after the onset of ALS	≤2 years	≤3 years	≤3 years	
%FVC	≥80%	≥70%	≥60%	

Table 12. Results of additional analysis in Study MCI186-16 (FAS, LOCF)[a)]

Additional patient criteria[b)]	Treatment group	No. of patients evaluated	ALSFRS-R score[c)]		Change [d) e)]	Comparison with placebo[e)]	
			Before cycle 1 of treatment	2 weeks after the final dose in cycle 6 or at discontinuation		Difference between the groups[f)]	*P* value
Applicable	Placebo group	29	42.1 ± 2.3	34.7 ± 8.9	-7.59 ± 1.34	3.01 [0.35, 5.67]	0.0270
	Edaravone group	39	42.5 ± 2.5	38.4 ± 5.1	-4.58 ± 1.55		
Not applicable	Placebo group	70	40.7 ± 3.1	35.3 ± 6.8	-5.54 ± 1.08	-0.57 [-2.55, 1.41]	0.5711
	Edaravone group	61	39.3 ± 3.4	33.2 ± 7.5	-6.11 ± 1.03		

a) Patients who completed at least the first 3 cycles of treatment (i.e., day 81 of treatment) were assessed.
b) Applicable: Among patients in the FAS, those who fall into "definite" or "probable" ALS in the El Escorial and Airlie House diagnostic criteria but who do not have score <1 in any items of the ALSFRS-R score or a %FVC of <80% before the first cycle of treatment.
Not applicable: Among patients in the FAS, patients other than those applicable to the above condition.
c) Mean ± standard deviation
d) Adjusted mean ± standard error
e) Based on an analysis of variance model using treatment group, the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4), initial symptoms (bulbar symptoms/limb symptoms), and the use of riluzole as factors.
f) Edaravone group minus placebo group [95% CI]

The applicant explained the benefits and risks of edaravone in patients who meet the following criteria 3.(ii).B.(3).1) to 3.(ii).B.(3).4); such patients were excluded from Study MCI186-19.

3.(ii).B.(3).1) Patients falling into "probable-laboratory-supported" ALS according to the El Escorial and Airlie House diagnostic criteria

The applicant explained as follows:

Study MCI186-16 (5.3.5.1-2) enrolled patients falling into "definite," "probable," or "probable-laboratory-supported" ALS according to the El Escorial and Airlie House diagnostic criteria.[20)] Table 13 outlines changes in ALSFRS-R score by diagnosis. In both the placebo and edaravone groups, the change from baseline tended to be smaller in patients with "probable-laboratory-supported" ALS than in those with "definite" or "probable" ALS, suggesting that edaravone may not be as effective in patients with "probable-laboratory-supported" ALS enrolld in this study as in the target patient population in Study MCI186-19 (5.3.5.1-1). However, patients with "probable-laboratory-supported" ALS are considered to be at an earlier stage of disease as compared with those with "definite" or "probable" ALS, and these patient populations do not differ essentially in terms of the presence of motor neuron degeneration. Also, an analysis of patients with "probable-laboratory-supported" ALS revealed a slower decrease in ALSFRS-R score in the edaravone group than in the placebo group. According to these findings, edaravone may be expected to slow down the progression of functional impairement in patients

with "probable-laboratory-supported" ALS as well.

The applicant also explained that, on the basis of the occurrence of adverse events in Study MCI186-16, the risk of edaravone treatment was not substantially higher in patients with "probable-laboratory-supported" ALS than in those with "definite" or "probable" ALS.

The applicant explained that it is of clinically significance to use edaravone in patients with a diagnosis of "probable-laboratory-supported" ALS according to the El Escorial and Airlie House diagnostic criteria.

Table 3. Changes in ALSFRS-R score in patient subgroups stratified by diagnosis according the El Escorial and Airlie House diagnostic criteria in Study MCI186-16 (FAS, LOCF)[a)]

Diagnosis according to Revised Escorial Criteria before the 1st cycle of treatment	Treatment group	No. of patients evaluated	Before cycle 1 of treatment[b)]	Change at 2 weeks after the final dose in cycle 6 or at discontinuation[c)]	Difference between the groups[d)]
Definite or probable ALS	Placebo group	71	40.8 ± 2.9	-7.43 ± 0.98	0.97 [-0.90, 2.84]
	Edaravone group	80	40.7 ± 3.6	-6.46 ± 0.99	
Probable-laboratory-supported ALS	Placebo group	27	41.9 ± 3.0	-2.47 ± 1.41	0.22 [-2.17, 2.62]
	Edaravone group	20	40.0 ± 2.9	-2.24 ± 1.38	

a) Patients who completed at least the first 3 cycles of treatment (i.e., day 81 of treatment) were assessed.
b) ALSFRS-R score (mean ± standard deviation)
c) Adjusted mean ± standard error
Based on an analysis of variance model using treatment group, the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4), initial symptoms (bulbar symptoms/limb symptoms), and the use of riluzole as factors.
d) Edaravone group minus placebo group [95% CI]

3.(ii).B.(3).2) Patients with a disease duration of more than 2 years

The applicant explained as follows:

Study MCI186-16 (5.3.5.1-2) enrolled patients with a disease duration of ≤3 years. As Table 14 shows, the difference in change in ALSFRS-R score between the edaravone and placebo groups tended to be larger in patients with a disease duration of >2 and ≤3 years while the change from baseline tended to be smaller in patients with this disease duration than in those with a disease duration of ≤2 years. The applicant decided not to include patients who have a disease duration of >2 years in Study MCI186-19 (5.3.5.1-1) for the reasons that a more homogenous patient population would be eligible for the study; and that among patients who meet the inclusion and exclusion criteria regarding baseline symptoms for Study MCI186-19, those with a disease duration of >2 years were expected to have a slower disease progression, and thus would not be suitable for efficacy assessment at month 6 of treatment. As the results of Study MCI186-16 (albeit in a limited number of patients) suggest that edaravone may slow down the progression of functional impairement even in patients with a disease duration of >2 years, edaravone is expected to be effective in this patient population as well.

The applicant also explained that, on the basis of the occurrence of adverse events in Study MCI186-16, the risk of treatment was not substantially higher in patients with a disease duration of >2 years than in those with ≤2 years.

The applicant explained that it is of clinically significance to use edaravone in patients with a disease duration of >2 years.

Table 4. Changes in ALSFRS-R score by disease duration in Study MCI186-16 (FAS, LOCF)[a)]

Disease duration at the beginning of cycle 1 of treatment	Treatment group	No. of patients evaluated	Before cycle 1 of treatment[b)]	Change at 2 weeks after the final dose in cycle 6 or at discontinuation[c)]	Difference between the groups[d)]
≤2 years	Placebo group	86	41.3 ± 2.8	-6.72 ± 0.94	0.32 [-1.37, 2.01]
	Edaravone group	80	41 ± 2.9	-6.40 ± 0.95	
>2 and ≤3 years	Placebo group	13	40.2 ± 3.4	-3.20 ± 2.45	0.73 [-3.39, 4.85]
	Edaravone group	20	38.6 ± 4.6	-2.47 ± 2.45	

a) Patients who completed at least the first 3 cycles of treatment (i.e., day 81 of treatment) were assessed.
b) ALSFRS-R score (mean ± standard deviation)
c) Adjusted mean ± standard error
Based on an analysis of variance model using treatment group, the change in ALSFRS-R score from the run-in period, initial symptoms (bulbar symptoms/limb symptoms), and the use of riluzole as factors.
d) Edaravone group minus placebo group [95% CI]

3.(ii).B.(3).3) Patients with grade ≥ 3 ALS according to Japanese ALS severity classification

The applicant explained the efficacy of edaravone in patients with advanced ALS as follows:
Since edaravone is considered to exert its effects by protecting neurons rather than by regenerating motor neurons to improve disease conditions, patients with grade ≥3 ALS according to the Japanese ALS severity classification,[17)] in whom many motor neurons are damaged or lost, are not expected to respond well to edaravone as compared with patients with milder ALS, and were thus excluded from Study MCI186-19 (5.3.5.1-1). However, as it has been proposed that oxidative stress, a major contributory factor to ALS pathology, continues to damage neurons from the early to late stages of the disease (Pollari E et al, *Front Cell Neurosci*, 8: 131, 2014), edaravone is expected to be effective to a certain extent in slowing disease progression in patient populations with different severity of ALS.

Patients with grade 3 ALS according to the Japanese ALS severity classification were excluded from the confirmatory studies (Study MCI186-19, Study MCI186-16 [5.3.5.1-2]), but were assessed in a separate exploratory study (5.3.5.1-4, Study MCI186-18). In Study MCI186-18, the mean absolute change in ALSFRS-R score was larger in the edaravone group than in the placebo group (Table 1), but this result is likely to be attributable to the data from a patient in the edaravone group who showed a substantial progression of the disease during the evaluation period (an ALSFRS-R score of 1 at the final assessment). Also, the median change in ALSFRS-R score, which is less likely to be affected by score of this patient, was −5.5 in the placebo group and −5.0 in the edaravone group, indicating that the absolute change was smaller in the edaravone group. Patients with grade 4 or 5 ALS according to the Japanese ALS severity classification were not assessed systematically as they were excluded from all clinical studies of edaravone because study participation and assessment using the ALSFRS-R were expected to be difficult. During the extension study (5.3.5.1-3, Study MCI186-17), some patients among those eligible for efficacy analysis based on the ALSFRS-R score showed a progression to grade 4 or 5 ALS according to the Japanese ALS severity classification; specifically, 3 patients in the MP group, 1

patients in the MM group, and 9 patients in the PM group showed a progression to grade 4 ALS by the beginning of cycle 7 of treatment; and 1 patients in the MP group, 0 patients in the MM group, and 7 patients in the PM group to grade 5 ALS by the beginning of cycle 13 of treatment. Since the number of eligible patients was small, a tendency toward slower progression was not clearly observed in patients receiving edaravone. Considering the pharmacological action of edaravone, the drug is unlikely to be effective for the degenerated or lost neurons. However, patients with grade 4 or 5 ALS according to the Japanese ALS severity classification may still have some movable parts of the body, and edaravone is expected to delay the loss of remaining physical function even though its effects may not be reflected to ALSFRS-R scores.

The applicant explained the safety of edaravone therapy as follows:
No substantial safety problems were observed in Study MCI186-18 in patients with grade 3 ALS according to the Japanese ALS severity classification. As the safety analysis of edaravone in patients with grade ≥4 ALS according to the Japanese ALS severity classification, Table 15 summarizes the occurrence of adverse events in patient subgroups stratified by severity grade in Study MCI186-17. The incidence of serious adverse events other than death and severe adverse events tended be high in patients with severe ALS. However, the number of patients with grade ≥4 ALS was limited. Also, the serious adverse events other than death and severe adverse events included dyslalia, respiratory failure, dysphagia, musculoskeletal disorder, and abasia, which are associated with the progression of ALS, and a causal relationship between these events and the study drug was ruled out.[16)] The applicant considered that there were no substantial safety problems in patients with grade ≥4 ALS according to the Japanese ALS severity classification.

Table 15. Occurrence of adverse events by Japanese ALS severity classification grade rated in Study MCI186-17

Evaluation period	Cycles 7-12						Cycles 13-15	
The Japanese ALS severity classification	Grade 1-3			Grade 4			Grade 1-4	Grade 5
Patients groups	MP group	MM group	PM group	MP group	MM group	PM group	Edaravone	Edaravone
No. of patients evaluated	42	45	76	3	2	11	151	9
Adverse events	90.5 (38)	88.9 (40)	84.2 (64)	100 (3)	100 (2)	100 (11)	64.9 (98)	77.8 (7)
Adverse drug reactions[a)]	4.8 (2)	4.4 (2)	10.5 (8)	0.0 (0)	0.0 (0)	0.0 (0)	2.6 (4)	0.0 (0)
Adverse events resulting in death	4.8 (2)	4.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)	9.1 (1)	1.3 (2)	0.0 (0)
Bronchopneumonia	0.0 (0)	2.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Pneumonia	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.7 (1)	0.0 (0)
Respiratory failure	4.8 (2)	2.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.3 (2)	0.0 (0)
Cardiac arrest	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	9.1 (1)	0.0 (0)	0.0 (0)
Serious adverse events other than death	16.7 (7)	33.3 (15)	26.3 (20)	0.0 (0)	100.0 (2)	90.9 (10)	18.5 (28)	55.6 (5)
Severe adverse events	11.9 (5)	26.7 (12)	26.3 (20)	0.0 (0)	100.0 (2)	81.8 (9)	15.9 (24)	44.4 (4)

Incidence (%) (number of subjects with the event)
a) Adverse events considered "probably" or "possibly" related to the study drug

On the basis of the results of Study MCI186-18, edaravone is expected to be effective in patients with

grade 3 ALS according to the Japanese ALS severity classification, and no substantial safety problems were observed. Thus, the use of edaravone in these patients is of clinically significance. On the other hand, since there is limited clinical experience with edaravone in patients with grade 4 or 5 ALS, it is difficult to demonstrate the efficacy of edaravone based on the clinical study results. However, given that no substantial safety problems were observed; that the mechanism of action of edaravone indicates the potential efficacy in patients with severe ALS; and that few therapies have been established for ALS, edaravone has certain clinical significance for this patient population on the premise that the safety of edaravone therapy is carefully monitored.

3.(ii).B.(3).4) Patients with a %FVC of <80%

The applicant explained as follows:

Since patients with a %FVC of <80% are considered in advanced stages as in patients with grade ≥3 ALS according to the Japanese ALS severity classification, they may not respond to edaravone as do milder patients. However, edaravone may be expected to slow down disease progression to some extent, in light of its mechanism of action [see "3.(ii).B.(3).3) Patients with grade ≥3 according to the Japanese ALS severity classification"]. Taking into account the results of Study MCI186-16 (5.3.5.1-2), the inclusion criteria regarding respiratory function for Study MCI186-19 (5.3.5.1-1) was established to enrol patients with milder ALS in the study by setting a higher %FVC level as the inclusion criteria for respiratory disorder.

In addition, Study MCI186-16 enrolled patients with a %FVC of ≥70%, and some participants had a %FVC of <70% at the beginning of Study MCI186-17 (5.3.5.1-3). Table 16 and Table 17 show changes in ALSFRS-R score in patient subgroups stratified by %FVC in Study MCI186-16 and Study MCI186-17, respectively. Symptoms tended to be more aggravated in patients receiving edaravone among patients with a %FVC of <80% in Study MCI186-16. However, the number of patients assessed was limited, and no clear conclusion was made in terms of the efficacy of edaravone in this patient population.

Table 5. Changes in ALSFRS-R score and %FVC in patient subgroups stratified by %FVC (≥80% vs. ≥70 and <80%) in Study MCI186-16 (FAS, LOCF)[a)]

Items of evaluation	%FVC at the beginning of cycle 1 of treatment	Treatment group	No. of patients evaluated	Before cycle 1 of treatment[b)]	Change at 2 weeks after the final dose in cycle 6 or at discontinuation[c)]	Difference between the groups[d)]
ALSFRS-R score	≥80%	Placebo group	74	41.3 ± 2.7	-5.93 ± 0.82	1.11 [-0.42, 2.63]
		Edaravone group	79	40.9 ± 3.6	-4.82 ± 0.86	
	≥70% <80%	Placebo group	25	40.5 ± 3.4	-6.69 ± 2.26	-2.62 [-6.53, 1.28]
		Edaravone group	21	39.1 ± 2.8	-9.31 ± 2.09	
%FVC	≥80%	Placebo group	74	102.67 ± 14.32	-18.23 ± 2.41	5.09 [0.60, 9.58]
		Edaravone group	79	100.89 ± 12.05	-13.14 ± 2.54	
	≥70% <80%	Placebo group	25	75.22 ± 3.57	-9.90 ± 6.53	-8.44 [-19.74, 2.86]
		Edaravone group	21	75.28 ± 3.06	-18.34 ± 6.05	

a) Patients who completed at least the first 3 cycles of treatment (i.e., day 81 of treatment) were assessed.
b) ALSFRS-R score or %FVC (mean ± standard deviation)
c) Adjusted mean ± standard error
Based on an analysis of variance model using treatment group, the change in ALSFRS-R score from the run-in period (-1 -2/-3, -4), initial symptoms (bulbar symptoms/limb symptoms), and the use of riluzole as factors.
d) Edaravone group minus placebo group [95% CI]

Table 17. Changes in ALSFRS-R score and %FVC in patient subgroups stratified by %FVC (≥70% vs. <70%, and ≥60% vs. <60%) in Cycles 7 to 12 of Study MCI186-17 (FAS, LOCF)[a)]

Items of evaluation	%FVC at the beginning of cycle 7 of treatment	Treatment groups	No. of patients evaluated	Before Cycle 7 of treatment[b)]	Change at 2 weeks after the final dose in cycle 12 or at discontinuation[c)]	Difference between the groups[d)]
ALSFRS-R score	≥70%	MP group	36	37.2 ± 5.4	-5.15 ± 0.75	
		MM group	35	37.1 ± 5.6	-3.70 ± 0.77	1.45 [-0.55, 3.45]
		PM group	58	38.2 ± 5.3	-5.05 ± 0.60	
	<70%	MP group	5	34.0 ± 5.7	-7.41 ± 2.24	
		MM group	9	34.3 ± 5.7	-6.66 ± 1.63	0.75 [-4.93, 6.43]
		PM group	22	31.9 ± 7.0	-7.37 ± 1.07	
%FVC	≥70%	MP group	36	95.03 ± 14.38	-9.20 ± 2.53	
		MM group	35	96.56 ± 11.96	-12.47 ± 2.59	-3.27 [-10.02, 3.47]
		PM group	58	93.40 ± 14.73	-13.30 ± 2.02	
	<70%	MP group	5	55.50 ± 15.28	-15.72 ± 6.03	
		MM group	9	56.36 ± 11.69	-15.45 ± 4.37	0.27 [-15.04, 15.58]
		PM group	20	58.89 ± 10.97	-7.34 ± 3.01	
ALSFRS-R score	≥60%	MP group	38	37.3 ± 5.3	-5.39 ± 0.75	
		MM group	41	36.9 ± 5.4	-3.89 ± 0.71	1.49 [-0.47, 3.46]
		PM group	72	37.5 ± 5.3	-5.36 ± 0.55	
	<60%	MP group	3	30.3 ± 3.8	-7.88 ± 2.36	
		MM group	3	32.3 ± 8.5	-9.96 ± 2.11	-2.08 [-8.82, 4.66]
		PM group	8	27.0 ± 8.5	-8.84 ± 1.30	
%FVC	≥60%	MP group	38	93.58 ± 15.33	-9.48 ± 2.34	
		MM group	41	91.75 ± 16.15	-12.73 ± 2.23	-3.25 [-9.39, 2.89]
		PM group	72	87.76 ± 17.59	-12.45 ± 1.72	
	<60%	MP group	3	47.57 ± 15.03	-23.39 ± 11.11	
		MM group	3	41.60 ± 5.65	-20.18 ± 9.67	3.22 [-28.93, 35.36]
		PM group	6	46.11 ± 12.64	-4.25 ± 6.97	

a) Patients who completed at least the first 9 cycles of treatment (i.e., day 249 of treatment) were assessed.
b) ALSFRS score or % FVC (mean ± standard deviation)
c) Adjusted mean ± standard error
Based on an analysis of variance model using treatment group and the change in ALSFRS-R score from the run-in period (-1, -2/-3, -4) as factors.
d) MM group minus MP group [95% CI]

The applicant's explaination about the safety of edaravone in patients with a %FVC of <80% was as follows:

Table 18 and Table 19 show the occurrence of adverse events in patient subgroups stratified by %FVC in Studies MCI186-16 and MCI186-17, respectively. The incidence of serious adverse events other than death and severe adverse events tended to be higher in patients with a %FVC of <80% than in those with a %FVC of ≥80%. Although the number of patients assessed was limited, most of the serious adverse events other than death and severe adverse events observed in patients with a %FVC of 60 to 80% were those associated with the progression of ALS, such as dyslalia, dyspnoea, respiratory disorder, respiratory failure, dysphagia, musculoskeletal disorder, and abasia, and a causal relationship between these events and the study drug was ruled out.[16)] In Study MCI186-16 and Study MCI186-17, the

incidence of adverse events related to respiratory disorders[41] tended to be higher in patients with decreased respiratory function than those without it, and this tendency was confirmed in both the placebo group and the MP group. These findings indicate that the difference in the incidence of respiratory adverse events by %FVC reflects the deterioration of respiratory function due to the progression of ALS, and a causal relationship between these events and the study drug was ruled out.[16]

Table 6. Occurrence of adverse events by % FVC (80%) in Study MCI186-16

%FVC at the beginning of Cycle 1 of treatment	≥80%		≥70% and <80%	
Treatment group	Placebo group	Edaravone group	Placebo group	Edaravone group
No. of patients evaluated	79	81	25	21
Adverse events	89.9 (71)	88.9 (72)	84.0 (21)	90.5 (19)
Adverse drug reactions[a)]	19.0 (15)	16.0 (13)	20.0 (5)	4.8 (1)
Adverse events resulting in death	1.3 (1)	0.0 (0)	4.0 (1)	14.3 (3)
respiratory disorder	0.0 (0)	0.0 (0)	0.0 (0)	9.5 (2)
respiratory failure	1.3 (1)	0.0 (0)	4.0 (1)	4.8 (1)
Serious adverse events other than death	20.3 (16)	7.4 (6)	28.0 (7)	52.4 (11)
Severe adverse events	21.5 (17)	8.6 (7)	20.0 (5)	42.9 (9)
Adverse events associated with respiratory disorder	38.0 (30)	30.9 (25)	40.0 (10)	52.4 (11)

Incidence (%) (number of subjects with the event)
a) Adverse events considered "probably" or "possibly" related to the study drug

Table 7. Occurrence of adverse events by % FVC (≥70% vs. <70%, and ≥60% vs. <60%) in Cycles 7 to 12 in Study MCI186-17

%FVC at the beginning of Cycle 7 of treatment	≥ 70%			< 70%			≥ 60%			< 60%		
Treatment group	MP group	MM group	PM group	MP group	MM group	PM group	MP group	MM group	PM group	MP group	MM group	PM group
No. of patients evaluated	38	36	62	7	12	26	40	42	76	5	6	12
Adverse events	92.1 (35)	86.1 (31)	83.9 (52)	85.7 (6)	91.7 (11)	92.3 (24)	92.5 (37)	88.1 (37)	85.5 (65)	80.0 (4)	83.3 (5)	91.7 (11)
Adverse drug reactions[a)]	5.3 (2)	2.8 (1)	11.3 (7)	0.0 (0)	8.3 (1)	7.7 (2)	5.0 (2)	4.8 (2)	9.2 (7)	0.0 (0)	0.0 (0)	16.7 (2)
Adverse events resulting in death	0.0 (0)	0.0 (0)	1.6 (1)	28.6 (2)	16.7 (2)	0.0 (0)	0.0 (0)	2.4 (1)	1.3 (1)	40.0 (2)	16.7 (1)	0.0 (0)
Bronchopneumonia	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	8.3 (1)	0.0 (0)	0.0 (0)	2.4 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Cardiac arrest	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Respiratory failure	0.0 (0)	0.0 (0)	0.0 (0)	28.6 (2)	8.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	40.0 (2)	16.7 (1)	0.0 (0)
Serious adverse events other than death	7.9 (3)	30.6 (11)	25.8 (16)	57.1 (4)	50.0 (6)	57.7 (15)	12.5 (5)	31.0 (13)	27.6 (21)	40.0 (2)	66.7 (4)	83.3 (10)
Severe adverse events	2.6 (1)	22.2 (8)	22.6 (14)	57.1 (4)	50.0 (6)	61.5 (16)	7.5 (3)	23.8 (10)	26.3 (20)	40.0 (2)	66.7 (4)	83.3 (10)
Adverse events associated with respiratory disorder	36.8 (14)	33.3 (12)	43.5 (27)	57.1 (4)	66.7 (8)	53.8 (14)	37.5 (15)	35.7 (15)	42.1 (32)	60.0 (3)	83.3 (5)	75.0 (9)

Incidence (%) (number of subjects with the event)
a) Adverse events considered "probably" or "possibly" related to the study drug

The applicant explained the efficacy and safety of edaravone in patients with tracheostomy as follows:

[41)] Adverse events related to respiratory disorders were defined as adverse events classified by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) into "respiratory, thoracic and mediastinal disorders" (but not including Preferred Terms [PTs] classified by High Level Group Term [HLGT] into "congenital respiratory tract disorders," "neonatal respiratory disorders," or "respiratory tract neoplasms"), those by MedDRA HLGT into "respiratory and pulmonary investigations (excl blood gases)," and those by MedDRA HLT into "blood gas and acid base analyses."

The package insert for riluzole contains precautions on the use of the drug for "patients who underwent tracheostomy" and provides related information. Since "patients who underwent tracheostomy" were excluded at the time of enrollment in the clinical studies of edaravone, and since "patients undergoing tracheostomy" was specified in the discontimuation criteria,[42)] no patients received edaravone after tracheostomy during the studies. The efficacy and safety of edaravone in patients who underwent tracheostomy have thus not been confirmed, but edaravone is expected to slow down the progression of ALS to some extent considering the pharmacological action of edaravone.

On the basis of the above findings, the applicant explained as follows:
Although the efficacy of edaravone has not been established in patients with a %FVC of <80%, the use of edaravone in such patients has certain clinical significance on the premise that the safety of edaravone therapy is carefully monitored, because (1) no substantial safety problems were observed; (2) the mechanism of action indicates a potential effect in this patient population; and (3) few therapies have been established for ALS.

PMDA considers as follows:
Considering that the efficacy of edaravone was not demonstrated in the confirmatory study 1 (Study MCI186-16) but was demonstrated in the confirmatory study 2 (5.3.5.1-1, Study MCI186-19) in which the strict inclusion criteria was set according to the results of subgroup analyses of the confirmatory study 1 to limit the type of patients to be enrolled in the study, the efficacy of edaravone has been confirmed only in the patient populations investigated in Study MCI186-19. Given that the number of ALS patients in Japan is limited, and that ALS patients show diverse clinical courses, it is unavoidable to place a certain limit on patients to detect statistically significant differences in endpoints between the edaravone and placebo groups in a feasible clinical study. PMDA's view on the clinical significance of the use of edaravone in patients excluded from Study MCI186-19 is as follows:

- On the basis of the results of exploratory studies other than Study MCI186-19, edaravone is expected to be effective in "patients with 'probable-laboratory-supported' ALS according to the El Escorial and Airlie House diagnostic criteria" and "patients with a disease duration of >2 years" to some extent, and no substantial safety problems were observed. Edaravone can therefore be indicated for these patient populations, on the premise that sufficient information on the pharmaceutical development and on the type of participants investigated in each clinical study is provided to healthcare professionals in clinical practice. Sufficient data on the efficacy and safety of edaravone in these patient populations should be accumulated in post-marketing surveillance.
- For "patients with grade ≥3 ALS according to the Japanese ALS severity classification" and "patients with a %FVC of <80%," who represent patients with advanced ALS, currently available data do not demonstrate the efficacy of edaravone. It is especially difficult to analyze efficacy in patients with grade 4 ALS or those with a %FVC of <70%, as there is little clinical experience with edaravone therapy in these patients. However, since no safety problems that hinder treatment with

[42)] Excluding the phase II study (5.3.5.2-1, Study MCI186-12).

edaravone have been suggested by now, and since ALS is a serious and fatal disease for which available treatments are limited, it is not clinically appropriate to specify a blanket rule that edaravone therapy should be discontinued upon progression of the disease. It should therefore be advised that the efficacy and safety of edaravone have not been established in these patients. Also, physicians should carefully examine the risk-benefit balance of edaravone before the drug is used in these patient populations, on the premise that (1) the applicant provides healthcare professionals with precautions and information on the pharmaceutical development, target patients in each clinical study, and the results of efficacy and safety assessment; (2) patients are monitored carefully for the safety of edaravone treatment; and (3) sufficient data on the efficacy and safety of edaravone in these patient populations are collected via post-marketing surveillance.

A final decision will be made on whether or not edaravone can be indicated for patient populations excluded from Study MCI186-19 and what kind of precautions and information should be provided, taking account of comments raised in the Expert Discussion.

3.(ii).B.(4) Safety of edaravone

PMDA requested the applicant to explain the safety profile of edaravone on the basis of the occurrence of adverse events in clinical studies.

The applicant summarized the adverse events reported in pivotal clinical studies[43] in patients with ALS (Table 20), and explained as follows:

Comparisons between the placebo and edaravone groups did not reveal a greater risk of adverse events in the edaravone group than in the placebo group in the double-blind phase of the confirmatory study 2 (5.3.5.1-1, Study MCI186-19), the confirmatory study 1 (5.3.5.1-2, Study MCI186-16), and the study in patients with grade 3 ALS according to the Japanese ALS severity classification (5.3.5.1-4, Study MCI186-18). No patients included in these studies experienced serious adverse events for which a causal relationship with the study drug could not be ruled out.[16), 28)] A comparison between the MP and MM groups in the extension study (5.3.5.1-3, Study MCI186-17) revealed that the incidence of deaths and other serious adverse events were statistically significantly higher in the MM group than in the MP group; and that many cases of deaths and other serious adverse events were related to primary disease, i.e., ALS;[44] and the incidence of deaths and other serious adverse events not related to ALS did not differ substantially between the MP group (5 of 45 patients, 11.1%) and the MM group (7 of 48 patients, 14.6%).

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[43] 5.3.5.1-1, Study MCI186-19; 5.3.5.1-2, Study MCI186-16; 5.3.5.1-3, Study MCI186-17; 5.3.5.1-4, Study MCI186-18

[44] Adverse events related to ALS were defined as events reported with descriptions of "aggravation of ALS," "aggravation of amyotrophic lateral sclerosis," or "progression of ALS."

Table 20. Outline of adverse events observed in pivotal clinical studies

	Study MCI186-19 (double-blind period)		Study MCI186-19 (open-label period)		Study MCI186-16		Study MCI186-17			Study MCI186-18	
Group/patients[a)]	P group	M group	PM patients	MM patients	P group	M group	MP group	MM group	PM group	P group	M group
No. of patients evaluated	68	69	58	65	104	102	45	48	88	12	13
Adverse events	83.8 (57)	84.1 (58)	82.8 (48)	81.5 (53)	88.5 (92)	89.2 (91)	97.8 (44)	91.7 (44)	92.0 (81)	100.0 (12)	92.3 (12)
Adverse drug reactions[b)]	7.4 (5)	2.9 (2)	5.2 (3)	6.2 (4)	19.2 (20)	13.7 (14)	4.4 (2)	10.4 (5)	10.2 (9)	8.3 (1)	23.1 (3)
Death	0.0 (0)	0.0 (0)	6.9 (4)	3.1 (2)	1.9 (2)	2.9 (3)	4.4 (2)	8.3 (4)	1.1 (1)	0.0 (0)	7.7 (1)
Serious adverse events[c)]	23.5 (16)	15.9 (11)	39.7 (23)	26.2 (17)	23.1 (24)	17.6 (18)	28.9 (13)	52.1 (25)	44.3 (39)	16.7 (2)	23.1 (3)
Adverse events leading to study discontinuation	7.4 (5)	1.4 (1)	10.3 (6)	3.1 (2)	7.7 (8)	2.9 (3)	6.7 (3)	18.8 (9)	9.1 (8)	0.0 (0)	7.7 (1)
Adverse drug reactions leading to study discontinuation[b)]	1.5 (1)	0.0 (0)	1.7 (1)	0.0 (0)	1.9 (2)	1.0 (1)	0.0 (0)	0.0 (0)	1.1 (1)	0.0 (0)	0.0 (0)

Incidence (%) (number of patients with the event)
a) P group = placebo group; M group = edaravone group
b) Adverse events considered "probably" or "possibly" related to the study drug (in Study MCI186-16, Study MCI186-17, and Study MCI186-18) or adverse events with "a reasonable possibility that the drug is related to the event" (Study MCI186-19)
c) Including deaths

Deaths and serious adverse events developed in the MM group with a ≥10% higher incidence than in the MP group were System Organ Class (SOC) "respiratory, thoracic and mediastinal disorders" (6 of 45 patients [13.3%] in the MP group, 12 of 48 patients [25.0%] in the MM group) and "general disorders and administration site conditions" (0 of 45 patients [0.0%] in the MP group, 5 of 48 patients [10.4%] in the MM group). Of the 12 patients in the MM group who experienced adverse events classified into SOC "respiratory, thoracic and mediastinal disorders," 7 were ≥65 years of age. The number of patients ≥65 years of age was larger in the MM group (20 patients) than in the MP group (9 patients). These findings suggest that the difference in the incidence of deaths and other serious adverse events may have been attributded to the difference in age distribution between the MM and MP groups. However, an analysis of the incidence of deaths and other serious adverse events by age in Study MCI186-17 and the open-label phase of Study MCI186-19 (Table 21), in both of which a similar treatment cycle was used, the incidence of respiratory failure tended to be higher in patients ≥65 years of age in the MM group in Study MCI186-17, while the incidence of deaths and other serious adverse events including respiratory adverse events did not tend to differ substantially between age subgroups in the open-label phase of Study MCI186-19. Study MCI186-17 and the open-label study phase of Study MCI186-19 differed in the number of treatment cycles and the inclusion and discontinuation criteria related to respiratory function, and these differences are likely to have affected the incidence of adverse events. However, given that the number of patients assessed was limited, and that there were no consistent trends among studies, the applicant considers that provision of an additional precaution about the use of edaravone in elderly patients is not necessary at present.

Table 21. Occurrence of death and other serious adverse events by age in Study MCI186-17 and the open-label study phase of Study MCI186-19

	Study MCI186-17						Study MCI186-19 (open-label study phase)			
	<65 years			≥65 years			<65 years		≥65 years	
	MP group	MM group	PM group	MP group	MM group	PM group	PM patients	MM patients	PM patients	MM patients
No. of patients evaluated	36	28	61	9	20	27	38	39	20	26
Serious adverse events[a)]	27.8 (10)	46.4 (13)	45.9 (28)	33.3 (3)	60.0 (12)	40.7 (11)	31.6 (12)	25.6 (10)	55.0 (11)	26.9 (7)
SOC "Respiratory, thoracic and mediastinal disorders"	11.1 (4)	17.9 (5)	14.8 (9)	22.2 (2)	35.0 (7)	11.1 (3)	15.8 (6)	12.8 (5)	20.0 (4)	7.7 (2)
Dyspnoea	5.6 (2)	7.1 (2)	3.3 (2)	0.0 (0)	5.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)	5.0 (1)	3.8 (1)
Hypercapnia	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	3.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Aspiration pneumonia	2.8 (1)	3.6 (1)	1.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	5.3 (2)	5.1 (2)	5.0 (1)	0.0 (0)
Respiratory arrest	0.0 (0)	0.0 (0)	1.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Respiratory disorder	2.8 (1)	3.6 (1)	1.6 (1)	0.0 (0)	5.0 (1)	3.7 (1)	7.9 (3)	7.7 (3)	5.0 (1)	3.8 (1)
Respiratory failure	2.8 (1)	3.6 (1)	8.2 (5)	11.1 (1)	25.0 (5)	3.7 (1)	2.6 (1)	2.6 (1)	10.0 (2)	0.0 (0)
Sputum retention	0.0 (0)	0.0 (0)	0.0 (0)	11.1 (1)	0.0 (0)	3.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence (%) (number of patients with the event)
a) Including death

Table 22 summarizes the occurrence of adverse events by baseline patient characteristics, based on pooled data (from cycles 1 to 6) from clinical studies of edaravone in ALS patients. An analysis of events that developed more commonly in the edaravone group than in the placebo group and that occurred at different frequency in subgroups of the characteristics revealed that these factors are unlikely to affect the safety profile of edaravone.

Table 8. Occurrence of adverse events by baseline patient characteristics in pooled data from Study MCI186-12,[a)] Study MCI186-16, or Study MCI186-19 [b)]

		Adverse events		Death		Serious adverse events other than death	
		Placebo	Edaravone	Placebo	Edaravone	Placebo	Edaravone
Sex	Male	86.4 (95/110)	84.7 (94/111)	1.8 (2/110)	1.8 (2/111)	18.2 (20/110)	14.4 (16/111)
	Female	85.5 (53/62)	91.4 (64/70)	0.0 (0/62)	1.4 (1/70)	29.0 (18/62)	18.6 (13/70)
Age	<65 years	87.2 (102/117)	89.1 (114/128)	1.7 (2/117)	1.6 (2/128)	17.9 (21/117)	12.5 (16/128)
	≥65 years	83.6 (46/55)	83.0 (44/53)	0 (0/55)	1.9 (1/53)	30.9 (17/55)	24.5 (13/53)
Weight[c)]	<57.0 kg	85.5 (71/83)	94.4 (84/89)	2.4 (2/83)	1.1 (1/89)	25.3 (21/83)	19.1 (17/89)
	≥57.0 kg	86.5 (77/89)	80.4 (74/92)	0 (0/89)	2.2 (2/92)	19.1 (17/89)	13.0 (12/92)
Initial symptoms	Bulbar symptoms	82.4 (28/34)	89.2 (33/37)	2.9 (1/34)	2.7 (1/37)	47.1 (16/34)	35.1 (13/37)
	Limb symptoms	87.0 (120/138)	86.8 (125/144)	0.7 (1/138)	1.4 (2/144)	15.9 (22/138)	11.1 (16/144)
Japanese ALS severity classification	Grade 1	85.7 (48/56)	83.3 (50/60)	1.8 (1/56)	1.7 (1/60)	16.1 (9/56)	10.0 (6/60)
	Grade 2	86.2 (100/116)	89.3 (108/121)	0.9 (1/116)	1.7 (2/121)	25.0 (29/116)	19.0 (23/121)
%FVC[c)]	≥95.8	89.2 (74/83)	86.2 (81/94)	0 (0/83)	0 (0/94)	16.9 (14/83)	4.3 (4/94)
	<95.8	83.1 (74/89)	88.5 (77/87)	2.2 (2/89)	3.4 (3/87)	27.0 (24/89)	28.7 (25/87)
Use of riluzole	Present	85.8 (133/155)	86.0 (141/164)	1.3 (2/155)	1.8 (3/164)	21.9 (34/155)	16.5 (27/164)
	Absent	88.2 (15/17)	100.0 (17/17)	0 (0/17)	0 (0/17)	23.5 (4/17)	11.8 (2/17)

Incidence (%) (number of patients with the event/number of patients assessed)
a) Patients who have grade 1 or 2 ALS according to the Japanese ALS severity classification before cycle 1 of treatment, and received edaravone at a dose of 60 mg
b) Double-blind phase
c) Stratified by median

On the basis of the above findings, the applicant explained that no substantial safety problems were found in ALS patients receiving edaravone, and there were no patient characteristics affecting the safety

profile of edaravone.

PMDA considers as follows:
The results of clinical studies indicate no major safety problems with edaravone. However, edaravone has been reported to carry the risk of renal impairment, hepatic dysfunction, and blood disorder associated with the treatment of acute cerebral infarction as the approved indication. Considering that patients with ALS, unlike those with acute cerebral infarction, are expected to receive edaravone repeatedly for a long period of time, a detailed review was made on the risk of renal impairment, hepatic dysfunction, and blood disorder associated with edaravone therapy, as well as the safety of long-term treatment with edaravone. Because Study MCI186-17 was not designed to allow patients to continue placebo treatment after Study MCI186-16, the analysis of the study results cannot predict factors that may affect the safety profile of edaravone. However, considering the available clinical study results, it cannot be ruled out that long-term treatment with edaravone may increase the risk of respiratory adverse events in elderly patients as compared with non-elderly patients. Accordingly, the package insert should include the precautions to the effect that careful administration is necessary in elderly patients with ALS, as in the current package insert, and healthcare professionals and ALS patients should be informed of the importance of careful respiratory management in ALS patients receiving edaravone through informative materials for healthcare professionals and patients to promote the proper use of the drug. The collection of information on the effects of baseline patient characteristics on the safety of edaravone should be continued in post-marketing surveillance.

3.(ii).B.(4).1) Risk of renal impairment
Cases of acute renal failure or aggravation of renal impairment have been reported in patients receiving edaravone for the treatment of acute cerebral infarction, and some of them led to the fatal outcome. Also, acute renal failure and nephrotic syndrome are described as clinically significant adverse reactions to edaravone in the package insert. On the basis of these facts, PMDA asked the applicant to explain the risk of renal impairment associated with edaravone therapy in ALS patients.

The applicant explained as follows:
The analysis of the pooled data (from cycles 1 to 12) from pivotal clinical studies of edaravone in ALS patients[45)] revealed the occurrence of adverse events related to renal impairment[46)] as shown in Table 23. The incidence of adverse events did not differ significantly between treatments during both of the periods from cycles 1 to 6 (between the placebo and edaravone groups) and from cycles 7 to 12 (among

[45)] The pooled analysis used data from cycles 1 to 6 in Study MCI186-12 (5.3.5.2-1, patients with a baseline Japanese ALS severity classification of 1 or 2 in the edaravone 60 mg group), Study MCI186-16 (5.3.5.1-2), and Study MCI186-19 (5.3.5.1-1, double-blind phase). Another pooled analysis used data from cycles 7 to 12 in Study MCI186-17 (5.3.5.1-3, cycles 7 to 12) and Study MCI186-19 (open-label phase).

[46)] Adverse events related to renal impairment were defined as adverse events classified by MedDRA SOC into "renal and urinary disorders" (except PTs under HLGT of "bladder and bladder neck disorders [excl calculi]" or "urolithiases"), those with a MedDRA HLGT of "renal and urinary tract investigations and urinalyses," and those with a MedDRA PT of "nephrotic syndrome," "blood albumin," "blood albumin abnormal," "blood albumin decreased," "hypoalbuminaemia," "protein total abnormal," or "protein total decreased."

the MP group, MM group, and PM group).[47] Severe or serious adverse events were observed in only 1 patient in the MM group (bladder cancer) during the period of cycles 7 to 12 of treatment, and a causal relationship of the event to edaravone treatment was ruled out.[16), 28)]

Table 9. Occurrence of adverse events related to renal impairment in pivotal clinical studies in ALS patients

Treatment cycle	Cycles 1-6		Cycles 7-12		
Treatment group	Placebo	Edaravone	MP	MM	PM
No. of patients evaluated	172	181	45	113	146
Adverse events related to renal impairment	7.0 (12)	6.6 (12)	6.7 (3)	8.8 (10)	9.6 (14)
Glucose urine present	1.7 (3)	3.3 (6)	0.0 (0)	0.9 (1)	1.4 (2)
Pollakiuria	1.2 (2)	1.1 (2)	2.2 (1)	2.7 (3)	1.4 (2)
Cystitis	1.2 (2)	1.1 (2)	2.2 (1)	0.9 (1)	0.0 (0)
Dysuria	0.6 (1)	0.6 (1)	0.0 (0)	0.0 (0)	2.1 (3)
Dehydration	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Blood urea increased	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Bladder cancer	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)
Blood urine present	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	2.7 (4)
Nocturia	0.6 (1)	0.0 (0)	0.0 (0)	2.7 (3)	0.0 (0)
Urinary tract infection	0.0 (0)	0.0 (0)	2.2 (1)	0.0 (0)	1.4 (2)
Incontinence	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.7 (1)
Haematuria	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.0 (0)
Protein urine present	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.7 (1)
Proteinuria	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence (%) (number of patients with the event)

The applicant explained as follows:

In Study MCI186-16 (5.3.5.1-2), Study MCI186-17 (5.3.5.1-3), and Study MCI186-19 (5.3.5.1-1), patients with renal impairment, which was defined as a creatinine clearance of ≤50 mL/min, were excluded. The pooled data (from cycles 1 to 12) from the pivotal clinical studies of edaravone in ALS patients[45)] revealed that no patients came to meet this criterion of renal impairment during the study. An increase in serum creatinine level by ≥0.3 mg/dL or 1.5-fold from baseline was observed in 0.6% (1 of 172) of patients in the placebo group and 0.6% (1 of 181) of patients in the edaravone group from cycles 1 to 6; and 2.2% (1 of 45) of patients in the MP group, 0.0% (0 of 113) of patients in the MM group, and 0.7% (1 of 146) of patients in the PM group from cycles 7 to 12. These findings indicate that edaravone does not affect renal function substantially.

Moreover, Table 24 summarizes the occurrence of adverse events related to renal impairment[46)] in the drug use-results survey of edaravone in patients with acute cerebral infarction. The incidence of such adverse events was 4.1% (162 of 3675) of patients receiving edaravone for <15 days[48)] and 0.3% (10 of 277) of those receiving edaravone for ≥15 days, indicating no increase in the incidence due to longer

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47) The MP group included patients who had been allocated to the edaravone group in Study MCI186-16 (5.3.5.1-2) and then to the placebo group in Study MCI186-17 (5.3.5.1-3).
The MM group included patients who had been allocated to the edaravone group in Study MCI186-16 and then to the edaravone group in Study MCI186-17, and patients who had received edaravone in the double-blind and open-label phases of Study MCI186-19 (5.3.5.1-1).
The PM group included patients who had been allocated to the placebo group in Study MCI186-16 and then to the edaravone group in Study MCI186-17, and patients who had received placebo in the double-blind phase and edaravone in the open-label phase of Study MCI186-19.

48) The recommended duration of edaravone therapy for acute cerebral infarction is "up to 14 days."

treatment durations. A comparison between the relevant results in patients with acute cerebral infarction and the occurrence of adverse events related to renal impairment (Table 23) in ALS patients based on the pooled data (cycles 1 to 6) from the pivotal clinical studies[45)] indicated no substantial increase in the risk of renal adverse events in ALS patients as compared with patients with acute cerebral infarction.

Table 24. Occurrence of adverse events related to renal impairment in the drug use-results survey in patients with acute cerebral infarction

No. of patients evaluated	3961
Adverse events related to renal impairment	4.4 (173)
Urinary tract infection	0.7 (29)
Renal impairment	0.7 (27)
Blood urine present	0.6 (25)
Protein total decreased	0.6 (25)
Blood urea increased	0.5 (20)
Blood creatinine increased	0.4 (15)
Protein urine present	0.4 (14)
Cystitis	0.3 (13)
Renal failure	0.3 (10)
Renal failure acute	0.2 (6)
Pyelonephritis	0.1 (4)
Haematuria	0.1 (4)
Proteinuria	0.1 (4)
Glucose urine present	0.1 (3)
Hypoalbuminaemia	0.1 (2)
Nephrotic syndrome	0.1 (2)
Renal infarct	0.1 (2)
Urine analysis abnormal	0.1 (2)
Azotaemia	0.0 (1)
Chromaturia	0.0 (1)
Glomerulonephritis chronic	0.0 (1)
Polyuria	0.0 (1)
Renal disorder	0.0 (1)
Bladder tamponade	0.0 (1)
Blood creatinine decreased	0.0 (1)
Blood urea decreased	0.0 (1)
Protein urine	0.0 (1)

Incidence (%) (number of patients with the event)

On the basis of the above findings, the risk of edaravone-associated renal impairment in ALS patients is unlikely to be clinically significant. The applicant claimed that no additional measures are necessary to address the risk as long as the precautions against renal impairment are specified as in the current package insert. However, edaravone is contraindicated in patients with serious renal impairment in the currently approved indication. There is no clinical experience of edaravone therapy in ALS patients with serious renal impairment, nor are safety data available in such patients. The severity and outcome of acute renal impairment associated with edaravone therapy in patients with acute cerebral infarction. Taking these facts into account, edaravone should be contraindicated also in ALS patients with serious renal impairment.

PMDA considers as follows:

The clinical study results provided by the applicant do not indicate a clear risk of renal impairment associated with edaravone therapy in ALS patients. However, considering the facts that there were patients who developed serious renal impairment associated with the use of edaravone for the treatment

of acute cerebral infarction and that patients with a prespecified level of renal impairment were excluded from clinical studies in ALS patients, edaravone should be contraindicated in ALS patients with serious renal impairment. In addition, precautions should be taken to ensure that renal function tests are periodically performed in ALS patients undergoing treatment with edaravone, and that edaravone therapy is discontinued and then appropriate care is provided if the patient has a decrease in renal function or symptoms such as oliguria, thereby enabling appropriate risk management. The possibility of an increased risk of renal impairment in ALS patients receiving edaravone should be continuously investigated via post-marketing surveillance.

3.(ii).B.(4).2) Risk of hepatic dysfunction

Cases of serious hepatic dysfunction have been reported in patients receiving edaravone for the treatment of acute cerebral infarction, and some of them led to the fatal outcome. Also, hepatitis fulminant, hepatic dysfunction and jaundice are listed as clinically significant adverse reactions to edaravone in the package insert to alert physicians. In addition, riluzole, a drug expected to be used concomitantly with edaravone, may increase the risk of hepatic dysfunction. On the basis of these facts, PMDA asked the applicant to explain the risk of renal impairment associated with edaravone therapy in ALS patients.

The applicant explained as follows:

Table 25 summarizes the occurrence of adverse events related to hepatic dysfunction[49)] based on the pooled data (from cycles 1 to 12) from pivotal clinical studies of edaravone in ALS patients,[45)] the incidence did not differ substantially between treatment groups during the period of cycles 1 to 6 or cycles 7 to 12. No patients experienced severe adverse events related to hepatic dysfunction, and serious adverse events occurred only in 2 patients in the placebo group during the period of cycles 1 to 6. The overall incidence of hepatic dysfunction based on the pooled data (from cycles 1 to 6) from pivotal clinical studies of edaravone in ALS patients was 5.9% (1 of 17) of patients in the placebo without riluzole group and 5.9% (1 of 17) of patients in the edaravone without riluzole group, and 5.8% (9 of 155) of patients in the placebo with riluzole group and 4.3% (7 of 164) of patients in the edaravone with riluzole group. Although a rigorous comparison between patients receiving study drug with and without riluzole cannot be made because of the limited number of patients receiving study drug without riluzole, the incidence of hepatic dysfunction did not differ substantially between with and without riluzole.

[49)] Adverse events categorized under a MedDRA HLGT of "hepatic and hepatobiliary disorders" or a HLT of "liver function analyses."

Table 10. Occurrence of adverse events related to hepatic function disorder in clinical studies in ALS

Treatment cycles	Cycles 1-6		Cycles 7-12		
Treatment group	Placebo	Edaravone	MP	MM	PM
No. of patients evaluated	172	181	45	113	146
Adverse events related to hepatic function disorder	5.8 (10)	4.4 (8)	2.2 (1)	0.9 (1)	3.4 (5)
Hepatic function abnormal	2.9 (5)	1.1 (2)	0.0 (0)	0.9 (1)	0.0 (0)
Liver disorder	0.0 (0)	1.1 (2)	0.0 (0)	0.0 (0)	2.1 (3)
Liver function test abnormal	0.6 (1)	1.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Hepatic steatosis	0.0 (0)	1.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Gamma-glutamyltransferase increased	0.0 (0)	0.6 (1)	2.2 (1)	0.0 (0)	0.7 (1)
Alanine aminotransferase increased	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.7 (1)
Ascites	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Drug-induced liver injury	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Aspartate aminotransferase increased	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Blood bilirubin increased	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Hypoproteinaemia	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence (%) (number of patients with the event)

The applicant also explained as follows:

Table 26 summarizes the overall incidence of liver function test abnormal based on the pooled data (from cycles 1 to 12) from the pivotal clinical studies of edaravone in ALS patients.[45)] The incidence of the event did not differ substantially between the treatment groups during the period of cycles 1 to 6 or cycles 7 to 12.

Table 11. Occurrence of abnormal liver function tests in clinical studies in ALS patients

Treatment cycles	Cycles 1-6		Cycles 7-12		
Treatment group	Placebo	Edaravone	MP	MM	PM
No. of patients evaluated	172	181	45	113	146
Liver function test abnormal	25.0 (43)	27.1 (49)	26.7 (12)	18.6 (21)	18.5 (27)
Total bilirubin ≥ UNL[a)]	21.5 (37)	25.4 (46)	26.7 (12)	15.9 (18)	17.1 (25)
ALT ≥ 3.0 × UNL[b)]	2.3 (4)	2.2 (4)	0.0 (0)	0.9 (1)	1.4 (2)
ALP ≥ 1.5 × UNL[c)]	3.5 (6)	1.1 (2)	0.0 (0)	1.8 (2)	0.7 (1)
AST ≥ 3.0 × UNL[d)]	0.6 (1)	1.1 (2)	0.0 (0)	1.8 (2)	0.0 (0)

Incidence (%) (number of patients with the event)
ALT = alanine aminotransferase; AST = aspartate aminotransferase;
ALP = alkaline phosphatase; UNL = upper normal limit
a) 1.2 mg/dL
b) 45 U/L (27 U/L in Study MCI186-12, 5.3.5.2-1)
c) 325 U/L (359 U/L in Study MCI186-12, 5.3.5.2-1)
d) 40 U/L (33 U/L in Study MCI186-12, in 5.3.5.2-1)

Table 27 summarizes the occurrence of adverse events related to hepatic dysfunction[49)] in the drug use-results survey of edaravone in patients with acute cerebral infarction. The overall incidence of adverse events related to hepatic dysfunction was 8.7% (343 of 3675) of patients receiving edaravone for <15 days[48)] and 0.7% (27 of 277) of those receiving edaravone for ≥15 days, indicating no increase in the incidence due to longer treatment durations. A comparison between the relevant results in patients with acute cerebral infarction and the occurrence of adverse events related to hepatic dysfunction (Table 25) in ALS patients based on the pooled data (from cycles 1 to 6) from the pivotal clinical studies[45)] indicated no substantial increase in the risk of adverse events related to hepatic dysfunction in ALS patients as compared with patients with acute cerebral infarction.

Table 12. Occurrence of adverse events related to hepatic dysfunction in the drug use-results survey in patients with acute cerebral infarction

No. of patients evaluated	3961
Adverse events related to hepatic function disorder	9.3 (370)
Hepatic function abnormal	4.4 (175)
Aspartate aminotransferase increased	2.4 (94)
Alanine aminotransferase increased	1.7 (68)
Gamma-glutamyltransferase increased	1.1 (42)
Liver disorder	0.7 (28)
Blood bilirubin increased	0.6 (25)
Hypoproteinaemia	0.3 (11)
Urobilinogen urine increased	0.3 (11)
Hepatic enzyme increased	0.1 (5)
Liver function test abnormal	0.1 (4)
Hypoalbuminaemia	0.1 (2)
Transaminases increased	0.1 (2)
Cirrhosis	0.0 (1)
Hepatic failure	0.0 (1)
Hepatitis	0.0 (1)
Hepatitis acute	0.0 (1)
Jaundice	0.0 (1)
Drug-induced liver injury	0.0 (1)
Aspartate aminotransferase decreased	0.0 (1)
Leucine aminopeptidase increased	0.0 (1)
Blood bilirubin decreased	0.0 (1)
Urine bilirubin increased	0.0 (1)

Incidence (%) (number of patients with the event)

On the basis of the above findings, the risk of edaravone-associated hepatic dysfunction in ALS patients is unlikely to be clinically significant. The applicant claimed that no additional measures are necessary to address the risk as long as the precautions against hepatic dysfunction are specifed as in the current package insert.

PMDA considers as follows:

The clinical study results provided by the applicant do not indicate a clear risk of hepatic dysfunction associated with edaravone therapy in ALS patients. However, considering the facts that there ware patients who developed serious hepatic dysfunction associated with the use of edaravone for the treatment of acute cerebral infarction and that many patients are expected to use edaravone in combination with riluzole, precautions should be taken to ensure that liver function tests are periodically performed in patients undergoing treatment with edaravone and that edaravone therapy is discontinued and then appropriate care is provied if abnormal liver test results are obtained from the patient, thereby enabling appropriate risk management. The possibility of an increased risk of hepatic dysfunction in ALS patients receiving edaravone should be continuously investigated via post-marketing surveillance.

3.(ii).B.(4).3) Risk of blood disorder

Cases of disseminated intravascular coagulation have been reported in patients receiving edaravone for the treatment of acute cerebral infarction, and some of them led to the fatal outcome. In addition, thrombocytopenia, granulocytopenia, and disseminated intravascular coagulation are listed as clinically significant adverse reactions to edaravone in the package insert. On the basis of these facts, PMDA asked the applicant to explain the risk of blood disorder associated with edaravone therapy in ALS

patients.

The applicant explained as follows:

Table 28 summarizes the occurrence of adverse events related to blood disorder[50] based on the pooled data (from cycles 1 to 12) from pivotal clinical studies of edaravone in ALS.[45] The overall incidence did not differ substantially between treatment groups during the period of cycles 1 to 6 or cycles 7 to 12. No patients experienced severe or serious adverse events related to blood disorder.

Table 28. Occurrence of adverse events related to blood disorder in pivotal clinical studies in ALS patients

Treatment cycles	Cycles 1-6		Cycles 7-12		
Treatment group	Placebo	Edaravone	MP	MM	PM
No. of patients evaluated	172	181	45	113	146
Adverse events related to blood disorder	3.5 (6)	1.7 (3)	0.0 (0)	2.7 (3)	2.1 (3)
Purpura	0.6 (1)	0.6 (1)	0.0 (0)	0.9 (1)	0.0 (0)
White blood cell count decreased	1.2 (2)	0.6 (1)	0.0 (0)	0.0 (0)	0.7 (1)
Henoch-Schonlein purpura	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Anaemia	2.3 (4)	0.0 (0)	0.0 (0)	0.9 (1)	0.7 (1)
White blood cell count increased	0.0 (0)	0.0 (0)	0.0 (0)	0.9 (1)	0.7 (1)

Incidence (%) (number of patients with the event)

The applicant explained as follows:

Table 29 summarizes the overall incidence of haematology test abnormal based on the pooled data (from cycles 1 to 12) from the pivotal clinical studies of edaravone in ALS patients.[45] Thrombocytopenia occurred only in the edaravone group. In 2 of the 3 patients with thrombocytopenia,[51] coagulation of the sample or erroneous testing procedures were suspected. In the remaining 1 patient, platelet count remained low from baseline to the end of the evaluation period. None of these patients had abnormal findings of other haematological parameters or signs of disseminated intravascular coagulation.

Table 13. Occurrence of abnormal blood test results in pivotal clinical studies in ALS patients

Treatment cycles		Cycles 1-6		Cycles 7-12		
Treatment group		Placebo	Edaravone	MP	MM	PM
No. of patients evaluated		172	181	45	113	146
Haematology test abnormal		26.2 (45)	26.0 (47)	17.8 (8)	24.8 (28)	25.3 (37)
Haematocrit ≤32% in women, and ≤37% in men		22.7 (39)	22.1 (40)	17.8 (8)	21.2 (24)	24.0 (35)
Haemoglobin ≤9.5 g/dL in women, and ≤11.5 g/dL in men		6.4 (11)	6.1 (11)	2.2 (1)	5.3 (6)	5.5 (8)
WBC ≤2.8 × 10^3/cells/mm^3		5.2 (9)	3.9 (7)	0.0 (0)	2.7 (3)	2.7 (4)
RBC <300 × 10^4/μL		1.7 (3)	1.1 (2)	0.0 (0)	0.9 (1)	2.1 (3)
Platelet	≤ 75 × 10^3/mm^3	0.0 (0)	1.7 (3)	0.0 (0)	0.9 (1)	0.0 (0)
	≥ 700 × 10^3/mm^3	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence (%) (number of patients with the event)

Table 30 summarizes the occurrence of adverse events related to blood disorder[50] in the drug use-results survey of edaravone in patients with acute cerebral infarction. The incidence of these adverse events

[50] Adverse events related to blood disorder were defined as adverse events classified by MedDRA HLGT under "anaemias nonhaemolytic and marrow depression," "haematological disorders NEC," "haemolyses and related conditions," "platelet disorders," "red blood cell disorders," "spleen, lymphatic and reticuloendothelial system disorders," "white blood cell disorders," "coagulopathies and bleeding diatheses (excl thrombocytopenic)," or "haematology investigations (incl blood groups)." Among adverse events categorized into "haematology investigations (incl blood groups)," those categorized under a HLT of "blood grouping and cross-matching analyses" were excluded.

[51] The 1 case during the period of cycles 1 to 6 and the 1 case during the period of cycles 7 to 12 developed in the same patient.

was 2.8% (111 of 3675) of patients receiving edaravone for <15 days[48)] and 0.3% (13 of 277) of those receiving edaravone for ≥15 days, indicating no increase in the incidence due to longer treatment durations. A comparison between the survey results in patients with acute cerebral infarction and the occurrence of adverse events related to blood disorder (Table 28) in ALS patients based on the pooled data (from cycle 1 to 6) from the clinical studies[45)] indicated no substantial increase in the risk of renal adverse events in ALS patients as compared with patients with acute cerebral infarction.

Table 14. Occurrence of adverse events related to blood disorder in the drug use-results survey in patients with acute cerebral infarction

No. of patients evaluated	3961
Adverse events related to blood disorder	3.2 (125)
Anaemia	0.9 (35)
White blood cell count increased	0.9 (35)
Platelet count decreased	0.4 (14)
Platelet count increased	0.3 (13)
Haemoglobin decreased	0.3 (13)
Red blood cell count decreased	0.3 (12)
Disseminated intravascular coagulation	0.3 (11)
Haematocrit decreased	0.3 (11)
White blood cell count decreased	0.2 (7)
Thrombocytopenia	0.1 (3)
Haematocrit increased	0.1 (2)
Jaundice	0.0 (1)
Haemoglobin abnormal	0.0 (1)
Leukocytosis	0.0 (1)
Haemoglobin increased	0.0 (1)
Coagulopathy	0.0 (1)
Red blood cell count increased	0.0 (1)

Incidence (%) (number of patients with the event)

On the basis of the above findings, the risk of edaravone-associated blood disorder in ALS patients is unlikely to be clinically significant. The applicant claimed that no additional measures are necessary to address the risk as long as the precautions against blood disorder are specified as in the current package insert.

PMDA considers as follows:

The clinical study results provided by the applicant do not indicate a clear risk of blood disorder associated with edaravone therapy in ALS patients. However, considering the fact that there were patients who developed serious blood disorder associated with the use of edaravone for the treatment of acute cerebral infarction, precautions should be taken to ensure that blood tests are periodically performed in patients undergoing treatment with edaravone, and that the treatment is discontinued and then appropriate care is provided if abnormal test results or symptoms suspected of disseminated intravascular coagulation are found, thereby enabling appropriate risk management. The possibility of an increased risk of blood disorder in ALS patients receiving edaravone should be continuously investigated via post-marketing surveillance.

3.(ii).B.(4).4) Long-term safety

PMDA asked the applicant to explain the long-term safety of edaravone.

The applicant explained as follows:

Table 31 summarizes the occurrence of adverse events and serious adverse events by cycle of treatment in patients who continued edaravone therapy in cycle 7 and the subsequent cycles (i.e., patients in the MM group in Study MCI186-17, 5.3.5.1-3; and patients in the MM group in Study MCI186-19, 5.3.5.1-1), the incidence of serious adverse events tended to increase in cycle 6 and the subsequent cycles. The most common adverse events included dyspnoea, respiratory disorder, respiratory failure, dysphagia, musculoskeletal disorder, and gait disturbance, but these events were considered to be associated with the progression of ALS. These findings indicate no problems in terms of the safety of repeated administration of edaravone in ALS patients.

Table 15. Occurrence of adverse events in each cycle of long-term treatment

Treatment cycle[a)]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
No. of patients evaluated	113	113	113	113	113	113	113	110	108	105	102	98	44	41	37
Adverse events	34.5 (39)	25.7 (29)	32.7 (37)	29.2 (33)	26.5 (30)	36.3 (41)	39.8 (45)	37.3 (41)	29.6 (32)	31.4 (33)	34.3 (35)	30.6 (30)	40.9 (18)	31.7 (13)	32.4 (12)
Serious adverse events [b)]	1.8 (2)	1.8 (2)	3.5 (4)	1.8 (2)	0.9 (1)	7.1 (8)	6.2 (7)	7.3 (8)	7.4 (8)	6.7 (7)	6.9 (7)	10.2 (10)	6.8 (3)	12.2 (5)	13.5 (5)
Common serious adverse events (observed in ≥2 patients in at least one course)															
Dyspnoea	-	-	-	-	-	0.9 (1)	2.7 (3)	0.9 (1)	-	-	-	-	2.3 (1)	-	-
Respiratory disorder	-	-	-	0.9 (1)	-	1.8 (2)	-	0.9 (1)	1.9 (2)	-	-	3.1 (3)	-	-	-
Respiratory failure	-	-	-	-	-	-	-	0.9 (1)	-	-	1.0 (1)	1.0 (1)	-	4.9 (2)	5.4 (2)
Dysphagia	0.9 (1)	-	2.7 (3)	0.9 (1)	0.9 (1)	4.4 (5)	0.9 (1)	1.8 (2)	1.9 (2)	3.8 (4)	1.0 (1)		-	9.8 (4)	2.7 (1)
Musculoskeletal disorder	-	0.9 (1)	-	-	-	-	-	0.9 (1)	2.8 (3)	1.9 (2)	2.0 (2)	3.1 (3)	-	-	2.7 (1)
Gait disturbance	-	-	-	-	-	-	-	0.9 (1)	-	-	-	2.0 (2)	2.3 (1)	-	-

Incidence (%) (number of patients with the event); - = 0.0% (0 patients)
a) Adverse events observed during the period from the day of first dose in each cycle to the end of the cycle were tabulated.
b) Including deaths

PMDA considers as follows:

Clinical study results submitted by the applicant indicate that serious adverse events tend to develop with an increased frequency in patients receiving edaravone repeatedly for long periods of time. As ALS progresses, respiratory dysfunction and weakness of limb muscles develop or progress in the patient. When edaravone is administered to a patient with ALS for a long period of time, the patient's condition should be monitored carefully to ensure the safety of treatment. The collection of data on the safety of long-term treatment with edaravone in ALS patients should be continued via post-marketing surveillance.

3.(ii).B.(5) Dosage and administration

PMDA asked the applicant to justify the proposed dosage and adminstration.

The applicant explained as follows:

Since ALS is a rare disease, it is very difficult to assess an optimal dose for ALS patients. Edaravone

protects neurons from oxidative stress by scavenging free radicals that may cause cellular damage, and this mechanism is expected to be effective both in patients with acute cerebral infarction and in those with ALS. Referring to the approved dose for the treatment of acute cerebral infarction (i.e., edaravone 30 mg twice daily by intravenous infusion over 30 minutes), the phase II clinical study (5.3.5.2-1, Study MCI186-12), which was the initial clinical study in ALS patients, was designed to administer edaravone once daily at a dose of 60 mg, equivalent to the daily dose for acute cerebral infarction, and at a dose of 30 mg, equivalent to half of the daily dose. Twice-daily adminitration of edaravone is recommended for the treatment of acute cerebral infarction, but a once-daily dosing regimen was selected for ALS patients to allow the participants to receive study treatment on an outpatient basis for the purpose of reducing burden on them. The applicant explained that the exposure in humans who receive edaravone 60 mg once daily by intravenous infusion over 60 minutes (estimates in healthy elderly individuals: C_{max}, 1023 ng/mL; $AUC_{0\text{-}24h}$, 1538 ng·h/mL[52)]) was not expected to differ substantially from the exposure in healthy elderly individuals who received edaravone 30 mg twice daily by intravenous infusion over 30 minutes (measured values in healthy elderly individuals: C_{max}, 1041 ng/mL; $AUC_{0\text{-}\infty}$, 1450 ng·h/mL). As the results of Study MCI186-12 suggested the efficacy of once-daily treatment with edaravone 60 mg with no substantial safety problems, the confirmatory studies (5.3.5.1-2, Study MCI186-16; 5.3.5.1-1, Study MCI186-19) were designed to administer edaravone 60 mg once daily by intravenous infusion over 60 minutes.

In the development program of edaravone for the treatment of acute cerebral infarction, edaravone was administered for 14 days to confirm the efficacy and safety of the drug, considering that tissue injury through the formation of free radicals and brain oedema persists for approximately 2 to 3 weeks after the onset of cerebral ischemia (the data submitted in the initial new drug application). Although the target disease is different, the applicant considered that the safety of ≤14-day treatment with edaravone had been established, and thus employed a treatment cycle of 14 days in studies in ALS patients. When the clinical studies of edaravone in ALS patients were designed, there were no data that were able to secure the safety of edaravone administered continuously for >14 days. Since *the Guidelines for Toxicity Studies of Drugs* describes that "for a drug which is administered intermittently at an interval of ≥2 weeks; whose treatment period is ≤2 weeks; and which does not accumulate substantially, the treatment period is considered to be ≤2 weeks" (Notification No. 655, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Welfare, dated April 5, 1999). Moreover, since it is not practical to continue once-daily administration by intravenous infusion for a prolonged period of time considering the burden on ALS patients, the applicant selected a cycle consisting of a 14-day treatment period followed by a 14-day rest period. In the clinical studies in ALS patients, the dosage regimen was designed to ensure convenience for participants. Specifically, the study drug was to be administered once daily for 14 days during the first cycle of treatment in hospital, and

[52)] The exposure after an intravenous infusion of edaravone 1mg/kg over 60 minutes was simulated using the pharmacokinetic parameters after the firstdose in a regimen of 0.5 mg/kg twice daily by intravenous infusion over 30 minutes for 2 days in healthy adult participants (C_{max}, 1041 ng/mL; $AUC_{0\text{-}\infty}$, 725 ng·h/mL; the data submitted in the initial new drug application).

then a total of 10 doses of the study drug were to be administered during a 14-day treatment period in the second and subsequent cycles as ambulatory treatment, because it was difficult for outpatients to receive intravenous infusions on Saturdays and Sundays.

The results of the confirmatory study 2 (5.3.5.1-1, Study MCI186-19) indicate that edaravone is effective in this patient population and its risk may not overweigh its safety as compared with the use of the drug in accordance with the already approved indication. Thus, the proposed dosage and administration of edaravone for the use in ALS patients should be the same as that used in Study MCI186-19, which is as follows: Edaravone 60 mg should be administered once daily over 60 minutes in cycles. In the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses should be administered during a 14-day period, followed by a 14-day rest period.

PMDA considers as follows:
The optimal dose of edaravone for ALS patients has not been investigated adequately. However, considering that the number of ALS patients in Japan is extremely small, and that items which can be investigated in clinical studies in ALS patients are limited, it is inevitable to set the dosage regimen employed in the clinical studies in ALS patients on the basis of the approved dosage regimen for the treatment of acute cerebral infarction, in the light of the mechanism of action of edaravone. Because ALS patients are expected to receive edaravone repeatedly for a relatively long period of time, physical and social burden related to edaravone therapy should be reduced as much as possible. Taking into account that the efficacy of edaravone in ALS patients has been demonstrated in Study MCI186-19, PMDA concluded that there should be no problem with setting the dosage and administration for the use in ALS patients based on the results of Study MCI186-19.

3.(ii).B.(6) Indications
PMDA asked the applicant to justify the proposed indication of edaravone.

The applicant explained as follows:
In the confirmatory study 2 in ALS patients (5.3.5.1-1, Study MCI186-19), a statistically significant difference was observed in changes in ALSFRS-R score from baseline, the primary endpoint, between the placebo and edaravone groups. A comparison of changes over time in ALSFRS-R score revealed that a course of 6 cycles of treatment (for approximately 6 months) with edaravone may slow down the progression of ALS-related functional impairement by approximately 2 months. The results of analysis of ALSAQ40, a secondary endpoint, indicated that edaravone may slow down the decrease in QOL in ALS patients [see "3.(ii).B.(2).1). Efficacy of edaravone in the confirmatory study 2" for details]. On the basis of these findings as well as the indications of riluzole, an approved ALS therapy, the proposed indication was set as "treatment of amyotrophic lateral sclerosis (ALS), and slowing of progression of amyotrophic lateral sclerosis (ALS), and reduction of the deterioration of the quality of life (QOL) (e.g.,

walking, activities of daily living, speech, and anxiety) associated with ALS."

However, the applicant reconsidered the proposed indication of edaravone and concluded that edaravone should be indicated for "slowing of progression of functional impairement in patients with amyotrophic lateral sclerosis (ALS)," because the indication should be based on the findings for the primary endpoint (ALSFRS-R) that demonstrated the efficacy of edaravone treatment, and because the drug is not a curative therapy of ALS but is expected to slow down the progression of functional impairement in ALS patients.

PMDA considers that edaravone should be indicated for "slowing of progression of functional impairement in patients with amyotrophic lateral sclerosis (ALS)," because the superiority of edaravone over placebo has been demonstrated in the change in ALSFRS-R, a rating scale of functional impairement. A final decision on the indication will be made, taking account of comments raised in the Expert Discussion.

3.(ii).B.(7) Post-marketing measures

In the clinical studies in patients with ALS, edaravone was administered in either the inpatient or outpatient setting. In cycle 7 and the subsequent cycles in Study MCI186-19 (5.3.5.1-1), 4 of 123 patients requested discontinuation of the study due to difficulty in visiting the clinic. Considering these facts, PMDA asked the applicant to explain how to treat ALS patients who develop difficulty in receiving outpatient treatment with edaravone in clinical practice due to disease progression.

The applicant explained as follows:

Since edaravone is administered by intravenous infusion and because the therapy may induce serious adverse events related to renal impairment, hepatic dysfunction, and blood disorder, the patients must be monitored by periodic tests, and thus outpatient treatment is basically desirable. However, additional measures to support home care would be necessary for patients who cannot visit a clinic due to the progression of ALS. The applicant is planning to take the following measures to ensure the proper use and safety of edaravone in ALS patients under home care:

- Edaravone should be administered to ALS patients in the home care setting only when ambulatory treatment is considered difficult by a physician with expertise in treating ALS (ALS specialist).
- Since edaravone is reported to increase the risk of renal impairment, hepatic dysfunction, and blood disorder in patients with acute cerebral infarction, ALS patients must receive the first cycle of edaravone therapy in the hospital setting. Requirements should be established for edaravone therapy in the home care setting, such as conducting laboratory tests to monitor renal and hepatic functions, and hematologic parameters at least once in the dosing period of each cycle.
- When home care physicians are involved in edaravone therapy, they should collaborate with ALS specialists to share the patient's information, including past treatment. A collaborative treatment plan

should be established to ensure that home care physicians can consult ALS specialists about treatment strategy, such as whether or not to continue edaravone therapy and how to deal with adverse events, and to ensure a system allowing ALS specialists to provide inpatient treatment or other necessary measures depending on the patient's condition.

- The attending physician should fully inform the patient who will start home care therapy and his/her family members of possible adverse drug reactions to edaravone in detail to ensure that they understand such adverse drug reactions.

The applicant plans to prepare informative materials on home care therapy so that a briefing session will be given to physicians and nurses involved in home care therapy to explain edaravone therapy using the materials and that the briefing session with the physician and nurses will be documented. Before home care therapy with edaravone is initiated, the applicant plans to ascertain the reason why the ALS specialist has determined that the patient cannot visit the clinic regularly to receive treatment, and to confirm that the patient is treated in the medical institution to which the ALS specialist belongs or other appropriate institutions in the event of development of serious adverse events such as renal impairment, hepatic dysfunction, and blood disorder. The applicant also intends to confirm that the home care physician has been given an explanation about edaravone therapy using the informative materials on the proper use of edaravone and on edaravone therapy in the home care setting.

PMDA considers as follows:
Edaravone should in principle be administered in the hospital setting, considering the route of administration and the safety profile of the drug. However, taking the pathological features of ALS into account, it is highly likely that edaravone therapy will have to be continued in ALS patients in the home care setting as the disease progresses. It is essential to develop and maintain a sufficient care system to ensure the safety of patients in the home care setting mainly on the basis of the measures proposed by the applicant. Risk minimization actions for home care therapy should be included in the risk management plan for edaravone, and the care system should be reconsidered when post-marketing safety information becomes available. The applicant proposed the measures in which a briefing session will be given to physicians and nurses involved in home care therapy to explain the resk management for edaravone therapy and the briefing session will be documented. However, such measures are not sufficient. It is necessary to not only conduct and document the briefing session but also to ensure that the healthcare professionals understand it fully.

Based on the results of the clinical studies in ALS patients and on the safety information obtained with the already approved indication, the applicant should investigate the occurrence of renal impairment, hepatic dysfunction, thrombocytopenia, granulocytopenia, disseminated intravascular coagulation syndrome, acute lung injury, rhabdomyolysis, shock/anaphylaxis, and nervous system disorder in association with edaravone therapy in ALS patients through post-marketing surveillance. The post-marketing surveillance should also be used to collect and analyze data on the effects of disease

progression on the occurrence of events as well as the effects of patient characteristics, e.g., the Japanese ALS severity classification grade and respiratory function, on the efficacy and safety of edaravone. The applicant plans to conduct a drug use-results survey in ALS patients with a target sample size of 700 and a follow-up period of 1 year for each patient (for up to 1.5 years on the occurrence of clinical events).

A final decision on the justification of these measures will be made taking account of comments raised in the Expert Discussion.

III. Results of compliance assessment concerning the data submitted in the new drug application and conclusion by PMDA

GCP on-site inspection is currently underway. The results and PMDA's conclusion will be reported in the Review Report (2).

IV. Overall Evaluation

Based on the data submitted by the applicant, PMDA has concluded that the efficacy of edaravone (Radicut) in the slowing of progression of functional impairement in patients with amyotrophic lateral sclerosis (ALS) has been demonstrated, and that its safety is acceptable in view of its observed benefits. Given that ALS is a serious and fatal disease and that currently available treatment options are extremely limited, edaravone will provide a new treatment option for ALS patients. It is therefore of clinical significance to make edaravone available for the new indication in clinical settings. The efficacy of edaravone was demonstrated in Study MCI186-19 (5.3.5.1-1), but the study had been conducted in a restricted patient population. Further review should be made at the Expert Discussion to determine the efficacy and safety in patients excluded from Study MCI186-19, whether or not edaravone can be used in such patients, and whether or not the precautions for the use is adequate.

PMDA has concluded that Radicut may be approved when Expert Discussions reveal no problems in this product.

Review Report (2)

May 18, 2015

I. Products submitted for registration

[Brand name]	(1) Radicut Injection 30 mg
	(2) Radicut Bag for Intravenous Infusion 30 mg
[Non-proprietary name]	Edaravone
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	October 29, 2014

II. Content of the review

The outline of the comments from the Expert Discussions and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussions were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

The expert advisors supported PMDA's conclusions described in the Review Report (1). PMDA conducted an additional review of the following points and took necessary actions.

(1) Safety monitoring and home care therapy

Since Radicut Injection 30 mg and Radicut Bag for Intravenous Infusion 30 mg (hereinafter collectively referred to as "Radicut") may cause serious adverse events related to renal impairment, hepatic dysfunction, and blood disorder, the expert advisors supported PMDA’s conclusion that patients receiving edaravone should be monitored by frequent, periodic blood tests for renal and hepatic functions and hematologic parameters. The expert advisors also supported the following PMDA's conclusions on edaravone therapy in the home care setting: (i) edaravone should in principle be administered in the hospital setting; (ii) an adequate care system should be developed and maintained to ensure the safety of patients receiving edaravone in the home care setting [see "3.(ii).B.(7) Post-marketing measures" of the Review Report (1)]; and (iii) the home care system should be re-examined when new post-marketing safety information becomes available. There was a comment from the expert advisors that it is difficult to assess renal function by comparing serum creatinine and blood urea nitrogen (BUN) levels between baseline and a single time point during treatment because muscle atrophy may cause a decrease in serum creatinine levels and dehydration, leading to fluctuation of BUN levels in patients with amyotrophic lateral sclerosis (ALS), and that a separate discussion should be made on how to assess renal function in ALS patients. In this regard, PMDA asked the applicant to discuss how

to assess renal function in ALS patients and to take appropriate measures.

The applicant consulted with nephrologists, and explained that the following procedures would be able to ensure the appropriate assessment of renal function in ALS patients with possible progressive muscle atrophy and should be included in the Important Precautions section of the package insert.

- Patients with ALS may show a decrease in serum creatinine levels induced by muscle atrophy associated with the progression of the disease. Thus, a comparison between the baseline value and the test value at a single time point during treatment is not sufficient to assess the renal function of ALS patients. Change over time in serum creatinine levels should be assessed to determine the presence/absence of a tendency toward disease progression. Since BUN levels may vary depending on total body water, a comparison between baseline value and the test value at a single time point during treatment is not sufficient. Change over time in BUN levels should be assessed to determine the presence/absence of a tendency toward disease progression.
- Patients with muscle atrophy should, at baseline and during edaravone therapy, undergo renal function tests for not only serum creatinine and BUN levels, but also the estimation of glomerular filtration rate using serum cystatin C level and the calculation of creatinine clearance from urine collection. The above tests and other tests are necessary to perform the renal function assessment that is not affected significantly by muscle volume.

The applicant also explained that patients receiving edaravone therapy even in the home care setting should be monitored for dehydration comprehensively based not only on BUN-to-creatinine ratio but also on physical findings of the patient. Patients should be examined by physicians before the beginning of each treatment cycle for the presence/absence of renal impairment, hepatic dysfunction, and blood disorder, as well as the presence/absence of dehydration. These precautions will be included in the safety measures for home care therapy.

PMDA accepts the above explanation and considers as follows:
The package insert and informative materials for the proper use of edaravone should include descriptions on how to assess renal function of ALS patients, so that precautions and information on edaravone therapy may be provided to all healthcare professionals who will use edaravone. When new findings on appropriate assessment of renal function in ALS patients become available through accumulating post-marketing safety information, the applicant should provide the information to healthcare professionals without delay.

(2) Use of edaravone in patients excluded from the confirmatory study 2 (5.3.5.1-1, Study MCI186-19)

At the Expert Discussion, the expert advisors supported PMDA’s conclusion that edaravone is expected to be effective to some extent in "patients with 'probable-laboratory-supported' ALS according to the El Escorial and Airlie House diagnostic criteria" and "patients with a disease duration of >2 years," with

no substantial safety problems. The expert advisors largely supported PMDA's conclusion that, although the efficacy and safety of edaravone have not been established in "patients with grade ≥3 ALS according to the Japanese ALS severity classification" (advanced ALS) or "patients with a percent predicted forced vital capacity (%FVC) of <80%," edaravone may be administered to these patient populations, on the premise that healthcare professionals are fully informed of the target patient populations in each clinical study and the results of these studies; that healthcare professionals are encouraged to carefully examine whether or not edaravone can be used in patients with grade ≥3 ALS according to the Japanese ALS severity classification and those with poor respiratory function; and that information on the efficacy and safety of edaravone in these patient populations is collected via post-marketing surveillance. There was a comment from the expert advisors that changes in scores for evaluation items of the ALS Functional Rating Scale-Revised (ALSFRS-R) by baseline score would be useful in evaluating the efficacy of edaravone in patients with advanced ALS, including those with grade ≥3 ALS according to the Japanese ALS severity classification. PMDA asked the applicant to explain this matter.

While presenting the percentage of patients with a decrease in the ALSFRS-R score who were tabulated for each item after stratification by baseline score based on the data from the confirmatory studies in ALS patients (5.3.5.1-1, Study MCI186-19; and 5.3.5.1-2, Study MCI186-16) (Tables 32 and 33), the applicant explained as follow:

Rigorous assessment is difficult because of the small number of patients evaluated and the great variability among individual patients, but the analysis suggested that edaravone tended to be more effective in slowing down disease progression in patients with higher scores at baseline.

Table 16. Percentage of patients with decrease in ALSFRS-R scores who were tabulated for each item after stratification by baseline score (Study MCI186-19, double-blind phase, FAS)

Baseline score[a)]	4		3		2	
Treatment group	Placebo group	Edaravone group	Placebo group	Edaravone group	Placebo group	Edaravone group
1. Speech	**19.4 (7/36)**	**7.7 (3/39)**	**45.8 (11/24)**	**33.3 (7/21)**	50.0 (3/6)	62.5 (5/8)
2. Salivation	**36.2 (17/47)**	**16.0 (8/50)**	**64.3 (9/14)**	**45.5 (5/11)**	20.0 (1/5)	71.4 (5/7)
3. Swallowing	**36.4 (16/44)**	**13.0 (6/46)**	**52.4 (11/21)**	**35.7 (5/14)**	**100.0 (1/1)**	**25.0 (2/8)**
4. Handwriting	**38.7 (12/31)**	**23.1 (9/39)**	9.1 (3/33)	11.5 (3/26)	0.0 (0/2)	66.7 (2/3)
5. Cutting food	**51.9 (14/27)**	**50.0 (13/26)**	**87.0 (20/23)**	**33.3 (7/21)**	50.0 (8/16)	66.7 (14/21)
6. Dressing and hygiene	**46.7 (7/15)**	**18.2 (2/11)**	**64.5 (20/31)**	**54.3 (19/35)**	**75.0 (15/20)**	**72.7 (16/22)**
7. Turning in bed	**48.6 (18/37)**	**35.0 (14/40)**	**70.0 (14/20)**	**45.8 (11/24)**	**44.4 (4/9)**	**25.0 (1/4)**
8. Walking	**50.0 (15/30)**	**19.4 (6/31)**	**69.2 (18/26)**	**37.0 (10/27)**	40.0 (4/10)	40.0 (4/10)
9. Climbing stairs	**52.6 (10/19)**	**19.2 (5/26)**	**95.0 (19/20)**	**25.0 (3/12)**	**66.7 (18/27)**	**63.3 (19/30)**
10. Respiration (1) Dyspnea[b)]	**21.2 (14/66)**	**16.2 (11/68)**				
10. Respiration (2) Orthopnea[b)]	**12.1 (8/66)**	**2.9 (2/68)**				
10. Respiration (3) Respiratory insufficiency[b)]	**1.5 (1/66)**	**0.0 (0/68)**				

Percentage (%) (Number of patients with a score lower than baseline score / Number of patients assessed for the item)

Bold: Items for which the percentage of patients with disease progression was lower in the edaravone group than in the placebo group.

a) At the time of enrollment in the study, patients with a baseline score of 1 in any evaluation item of the ALSFRS-R were excluded from the study.

b) At the time of enrollment in the study, patients with a baseline score of ≤3 in any of the 3 items of Respiration (1) to (3) were excluded from the study.

Table 17. Percentage of patients with decrease in ALSFRS-R scores who were tabulated for each item after stratification by baseline score (Study MCI186-16, FAS)

Baseline score	4		3		2		1	
Treatment group	Placebo group	Edaravone group	Placebo group	Edaravone group	Placebo group	Edaravone group	Placebo group	Edaravone group
1. Speech	17.7 (11/62)	19.3 (11/57)	38.5 (10/26)	41.4 (12/29)	62.5 (5/8)	72.7 (8/11)	0.0 (0/2)	100.0 (3/3)
2. Salivation	**27.6 (21/76)**	**18.9 (14/74)**	**50.0 (6/12)**	**45.5 (5/11)**	44.4 (4/9)	50.0 (6/12)	0.0 (0/2)	66.7 (2/3)
3. Swallowing	**24.6 (16/65)**	**23.3 (14/60)**	**51.6 (16/31)**	**31.3 (10/32)**	**50.0 (1/2)**	**33.3 (2/6)**	0.0 (0/1)	50.0 (1/2)
4. Handwriting	**43.8 (21/48)**	**36.4 (16/44)**	**35.0 (14/40)**	**29.5 (13/44)**	**62.5 (5/8)**	**50.0 (4/8)**	**50.0 (1/2)**	**0.0 (0/1)**
5. Cutting food	21.9 (7/32)	48.6 (17/35)	**55.9 (19/34)**	**38.2 (13/34)**	56.0 (14/25)	61.9 (13/21)	14.3 (1/7)	60.0 (6/10)
6. Dressing and hygiene	**42.9 (9/21)**	**40.0 (10/25)**	**61.5 (24/39)**	**61.1 (22/36)**	63.3 (19/30)	69.7 (23/33)	42.9 (3/7)	60.0 (3/5)
7. Turning in bed	38.5 (20/52)	40.8 (20/49)	**65.8 (25/38)**	**48.5 (16/33)**	**44.4 (4/9)**	**37.5 (6/16)**	- (0/0)	0.0 (0/2)
8. Walking	**34.8 (16/46)**	**28.2 (11/39)**	**46.9 (15/32)**	**40.5 (17/42)**	33.3 (7/21)	57.9 (11/19)	- (0/0)	- (0/0)
9. Climbing stairs	**45.0 (18/40)**	**40.0 (14/35)**	64.7 (11/17)	76.5 (13/17)	**72.0 (18/25)**	**63.3 (19/30)**	61.5 (8/13)	70.0 (7/10)
10. Respiration (1) Dyspnea[a)]	20.2 (20/99)	25.0 (25/100)						
10. Respiration (2) Orthopnea[a)]	**9.1 (9/99)**	**9.0 (9/100)**						
10. Respiration (3) Respiratory insufficiency[a)]	**8.1 (8/99)**	**3.0 (3/100)**						

Percentage (%) (Number of patients with a score lower than baseline score / Number of patients assessed for the item)
Bold: Items for which the percentage of patients with disease progression was lower in the edaravone group than in the placebo group.
a) At the time of enrollment in the study, patients with a baseline score of ≤3 in any of the 3 items of Respiration (1) to (3) were excluded from the study.

The applicant presented the corresponding percentages of patients in Study MCI186-18 (5.3.5.1-4) in patients with ALS of grade 3 according to the Japanese ALS severity classification (Table 34) and explained as follows:

These findings showed that among patients with a baseline score of 4 in terms of speech, salivation, or swallowing, those with a decrease in each score were lower in percentage in the edaravone group than in the placebo group, suggesting that edaravone tends to maintain each of the functions. Since the number of patients assessed for each score was very limited in Study MCI186-18, the applicant conducted an additional analysis in patients with a baseline score of ≥1. In 7 of the 12 items, the percentage of worsened patients was lower in the edaravone group than in the placebo group.

Table 34. Percentage of patients with decrease in ALSFRS-R scores who were tabulated for each item after stratification by baseline score (Study MCI186-18, FAS)

Baseline score	4		3		2		1		≥1	
Treatment group	Placebo group	Edaravone group	Placebo group	Edaravone group	Placebo group	Edaravone group	Placebo group	Edaravone group	Placebo group	Edaravone group
1. Speech	**50.0 (5/10)**	**20.0 (1/5)**	0.0 (0/2)	60.0 (3/5)	- (0/0)	50.0 (1/2)	- (0/0)	- (0/0)	41.7 (5/12)	41.7 (5/12)
2. Salivation	**25.0 (3/12)**	**11.1 (1/9)**	- (0/0)	0.0 (0/1)	- (0/0)	0.0 (0/2)	- (0/0)	100.0 (1/1)	**25.0 (3/12)**	**15.4 (2/13)**
3. Swallowing	**60.0 (6/10)**	**33.3 (3/9)**	0.0 (0/1)	66.7 (2/3)	0.0 (0/1)	100.0 (1/1)	- (0/0)	- (0/0)	**50.0 (6/12)**	**46.2 (6/13)**
4. Handwriting	33.3 (1/3)	50.0 (1/2)	**33.3 (1/3)**	**16.7 (1/6)**	66.7 (2/3)	100.0 (1/1)	**100.0 (1/1)**	**33.3 (1/3)**	**50.0 (5/10)**	**33.3 (4/12)**
5. Cutting food	**100.0 (1/1)**	**0.0 (0/1)**	50.0 (2/4)	50.0 (2/4)	0.0 (0/2)	50.0 (1/2)	66.7 (2/3)	100.0 (2/2)	50.0 (5/10)	55.6 (5/9)
6. Dressing and hygiene	- (0/0)	- (0/0)	0.0 (0/1)	33.3 (1/3)	**100.0 (3/3)**	**0.0 (0/1)**	**100.0 (5/5)**	**60.0 (3/5)**	**88.9 (8/9)**	**44.4 (4/9)**
7. Turning in bed	0.0 (0/1)	- (0/0)	**100.0 (3/3)**	**25.0 (1/4)**	**50.0 (1/2)**	**40.0 (2/5)**	**33.3 (2/6)**	**0.0 (0/3)**	**50.0 (6/12)**	**25.0 (3/12)**
8. Walking	**100.0 (3/3)**	**0.0 (0/1)**	50.0 (1/2)	60.0 (3/5)	33.3 (1/3)	33.3 (1/3)	0.0 (0/4)	0.0 (0/3)	**41.7 (5/12)**	**33.3 (4/12)**
9. Climbing stairs	- (0/0)	- (0/0)	**80.0 (4/5)**	**0.0 (0/1)**	- (0/0)	66.7 (2/3)	0.0 (0/1)	40.0 (2/5)	**66.7 (4/6)**	**44.4 (4/9)**
10. Respiration (1)[a)b)]	16.7 (2/12)	30.8 (4/13)							16.7 (2/12)	30.8 (4/13)
10. Respiration (2)[a)b)]	0.0 (0/12)	23.1 (3/13)							0.0 (0/12)	23.1 (3/13)
10. Respiration (3)[a)b)]	0.0 (0/12)	23.1 (3/13)							0.0 (0/12)	23.1 (3/13)

Percentage (%) (Number of patients with a score lower than baseline score / Number of patients assessed for the item)
Bold: Items of which the percentage of patients with disease progression was lower in the Edaravone group than in the placebo group.
a) Respiratory (1), assessed dyspnea; Respiratory (2), orthopnea; and Respiratory (3), respiratory failure.
b) At the time of enrollment in the study, patients with a baseline score of ≤3 in any of the 3 items of Respiration (1) to (3) were excluded from the study.

PMDA considers as follows:
Findings summarized in Tables 32 to 34 suggest that edaravone may be more effective in patients with less deteriorated functions. Edaravone is likely to be effective for items preserving a certain level of function even in patients with grade ≥3 (advanced) ALS according to the Japanese ALS severity classification, but it is difficult to make definitive conclusions from this analysis because the number of patients assessed for each item of the ALSFRS-R at baseline was small. These data do not demonstrate the efficacy of edaravone in patients with grade ≥3 ALS according to the Japanese ALS severity classification. Accordingly, in order to assess the efficacy of edaravone in patients with grade ≥3 (advanced) ALS according to the Japanese ALS severity classification or with poor respiratory function, sufficient information should be collected via post-marketing surveillance. The collected data should be analyzed using methods such as a comparison with an appropriately matched external control, and feedback should be provided to healthcare professionals in clinical practice.
The above conclusion of PMDA was supported by the expert advisors.

(3) Dosage and administration

At the Expert Discussion, the expert advisors supported the basic concept on the dosage and administration of edaravone (Radicut) [see "3.(ii).B.(5) Dosage and administration" in the Review Report (1)].

PMDA concluded that the following statements of the dosage and administration would be appropriate to clarify the different regimens for the first cycle and for the second and subsequent cycles.

[Dosage and Administration]
(a) Radicut Injection 30 mg:
The usual adult dosage is 60 mg of edaravone (2 ampoules) administered once daily by intravenous infusion over 60 minutes. Edaravone should be diluted with an appropriate volume of normal saline or other suitable diluent prior to administration.
Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. Usually, in the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily eradavone should be administered during a 14-day period, followed by a 14-day rest period.

(b) Radicut Bag for Intravenous Infusion 30 mg:
The usual adult dosage is 60 mg of edaravone (2 bags) administered once daily by intravenous infusion over 60 minutes.
Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. Usually, in the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily eradavone should

be administered during a 14-day period, followed by a 14-day rest period.

(4) Risk management plan (draft)

Taking account of the review described in "3.(ii).B.(7) Post-marketing measures of the Review Report (1)" and the comments from the Expert Discussion, PMDA has concluded that the safety specifications and efficacy concerns listed in Table 35 should be included in the draft risk management plan, and additional pharmacovigilance activities and risk minimization actions should be conducted as shown in Table 36.

Table 18. Safety specifications and efficacy concerns in the draft risk management plan

Safety Specifications		
Important identified risks	Important potential risks	Important missing information
• Renal impairment (acute renal failure, nephrotic syndrome) • Hepatic dysfunction (e.g., serious hepatitis such as hepatitis fulminant, hepatic dysfunction, and jaundice) • Thrombocytopenia, granulocytopenia • Disseminated intravascular coagulation (DIC) • Acute lung injury • Rhabdomyolysis • Shock and anaphylaxis	• Degeneration of neurons	• Results of edaravone therapy in patients with grade ≥3 ALS according to the Japanese ALS severity classification and those with poor respiratory function
Efficacy Concerns		
• Effects on long-term outcome of ALS		

Table 19. Outline of additional pharmacovigilance activities and additional risk minimization actions in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization actions
• Early post-marketing phase vigilance in ALS patients • Drug use-results survey in ALS patients	• Early post-marketing phase vigilance in ALS patients • Preparing and providing informative materials for healthcare professionals (guidance for proper use of edaravone) in ALS patients • Preparing and providing informative materials for patients (guidance for proper use of edaravone) in ALS patients • Safety measures for patients receiving Radicut in the home care setting.

On the basis of the above, PMDA requested the applicant to conduct post-marketing surveillance to assess the above matters.

The applicant explained as follows:

The specified drug use-results survey in ALS patients who are to receive edaravone will be conducted as shown in Table 37, and the effects of edaravone on the long-term outcome of patients in terms of the occurrence of any event specified in Clinical Events (1) and (2) will be investigated using methods such as comparison with appropriately matched external controls. On the assumption that patients with grade ≥3 ALS according to the Japanese ALS severity classification and those with a %FVC of <80% would account for approximately 50% of 700 patients to be enrolled in the survey, the applicant considers that

assessment of the long-term outcome of these patient populations would be possible.

Table 37. Draft outline of specified drug use-results survey

Purpose	Collect and evaluate data on the safety and efficacy of edaravone (Radicut) and long-term outcome of ALS patients in routine clinical settings
Survey method	Central registry system
Patients	ALS patients with no history of treatment with edaravone
Follow-up period	Up to 5 years[a)]
Planned number of patients	700 patients (number of patients to be enrolled)[b)]
Major survey items	• Patient characteristics (e.g., sex, age, body weight, in/outpatient status, complications, disease duration, initial symptoms, sporadic/familial ALS, disease type, diagnosis according to the El Escorial and Airlie House diagnostic criteria, Japanese ALS severity classification grade, %FVC and ALSFRS-R score at baseline) • Treatment with Radicut (e.g., daily dose, duration of treatment, number of doses given in each cycle, inpatient/outpatient/home care status) • Concomitant drug or therapy • Occurrence of adverse events • Clinical laboratory tests • Date of occurrence of Clinical Events (1) (i.e., death, permanent use of mechanical ventilation) • Date of occurrence of Clinical Events (2) (i.e., introduction of tube feeding, gastrostomy, indirect noninvasive ventilation assistance, tracheostomy, loss of speech, loss of swallowing, loss of upper limb function, loss of independent walking, or loss of independent turning on the bed) • ALSFRS-R

a) The safety of edaravone and use of concomitant drugs other than "drugs related to ALS treatment" will be monitored for 1 year. The ALSFRS-R, occurrence of Clinical Events (2), and use of "drugs related to ALS treatment" not for the purpose of slowing of disease progression will be monitored for 1.5 years. Patients will be followed for Clinical Events (1) for up to 5 years after the first dose of Radicut even in patients who discontinued Radicut therapy (However, the survey must include patients who have completed at least 3 cycles of treatment).

b) On the basis of the results of clinical studies, approximately 10% of the patients enrolled will annually drop out of the survey. If 350 patients with grade 1 or 2 ALS according to the Japanese ALS severity classification are enrolled, 300 patients will be able to be followed for 1.5 years and 200 patients for 5 years. When 188 patients are analyzed, a difference in the incidence of any event of Clinical Events (1) from the external control may be detected (with a power of 80%) when it is assumed that the 2-year survival in patients with grade 1 or 2 ALS according to the Japanese ALS severity classification will be 60%, and the survival will be prolonged by 0.5 years (hazard ratio of 0.7%). When 228 patients are analyzed, a difference in the incidence of any event of Clinical Events (2) from the external control may be detected (with a power of 80%) when it is assumed that event-free rate will be 40% and the hazard ratio will be 0.7.

PMDA accepted the above explanations, and concluded that the survey should be conducted without delay to confirm the efficacy and safety of Radicut (edaravone) in slowing down the progression of functional impairment in ALS patients, and findings should be provided to healthcare professionals in clinical practice in a timely manner.

III. Results of compliance assessment concerning the data submitted in the new drug application and conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

The document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. PMDA concluded that there should be no major problems with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

The GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-2, 5.3.5.1-3, and 5.3.5.1-4). As a result, PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted data. The following iregularities were found in some of the medical institutions conducting clinical studies of edaravone and communicated to the head of the relevant medical institution as areas for improvement, although such irregularities will not affect the assessment of the clinical studies as a whole.

[Areas for improvement]

Medical institutions

- Inappropriate operation of the institutional review board (failure to meet conditions for expedited review)
- Protocol violations (ASLFRS-R assessment by sub-investigators who did not undergo the relevant training; violations of rules for administration of study drug; testing beyond the acceptable range of dates; violations of criteria for study discontinuation)

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that Radicut (edaravone) may be approved with the indications and the dosage and administration modified as shown below, and with the following conditions. This application has been submitted for Radicut as an orphan drug, the re-examination period of Radicut for the new indication and dosage and administration to be added is 10 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and Radicut is not classified as a biological product or a specified biological product.

[Indications]

1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke
2. Slowing of progression of functional impairment in patients with amyotrophic lateral sclerosis (ALS)

(The underlined text denotes additions in this application.)

[Dosage and administration]

(a) Radicut Injection 30 mg

1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairment associated with acute ischemic stroke

The usual adult dosage is 30 mg of edaravone (1 ampoule) administered twice daily by intravenous infusion over 30

minutes in the morning and the evening. Edaravone should be diluted with an appropriate volume of normal saline or other suitable diluent prior to administration.

Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days.

2. Slowing of progression of functional impairement in patients with amyotrophic lateral sclerosis (ALS)

The usual adult dosage is 60 mg of edaravone (2 ampoules) administered once daily by intravenous infusion over 60 minutes. Edaravone should be diluted with an appropriate volume of normal saline or other suitable diluent prior to administration.

Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. Usually, in the first cycle, edaravone should be administered for 14 consecutive days, followed by a 14-day rest period. In the second and subsecuent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day period, followed by a 14-day rest period.

(b) Radicut Bag for Intravenous Infusion 30 mg,

1. Improvement of neurological symptoms, disability in activities of daily living, and functional impairement associated with acute ischemic stroke

The usual adult dosage is 30 mg of edaravone (1 bag) administered twice daily by intravenous infusion over 30 minutes in the morning and the evening.

Treatment with edaravone should be initiated within 24 hours after the onset of the disease and can be continued for up to 14 days.

2. Slowing of progression of functional impairement in patients with amyotrophic lateral sclerosis (ALS)

The usual adult dosage is 60 mg of edaravone (2 bags) administered once daily by intravenous infusion over 60 minutes.

Edaravone should be administered in cycles, each consisting of a treatment period and a rest period. Usually, in the first cycle, edaravone should be administered for 14 consecutive days,

followed by a 14-day rest period. In the second and subsequent cycles, a total of 10 doses of once-daily edaravone should be administered during a 14-day period, followed by a 14-day rest period.

(The underlined text denotes additions in this application.)

[Conditions for approval] The applicant is required to develop a risk management plan and implement it appropriately.