CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209176Orig1s000

MEDICAL REVIEW(S)

***** ATTENTION *****

The following primary clinical review dated May 2, 2017 for RADICAVA (edaravone) under NDA 209176 supersedes the primary clinical review dated February 2, 2017, and should be considered the clinical review of record for this NDA.

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	209176
Priority or Standard	Standard
Submit Date(s)	6/16/16
Received Date(s)	6/16/16
PDUFA Goal Date	6/6/17
Division/Office	ODE1 / DNP
Reviewer Name(s)	Christopher D. Breder, MD PhD
Review Completion Date	05/02/2017
Established Name	edaravone
Trade Name	RADICAVA
Applicant	Mitsubishi Tanabe Pharma Corporation
Formulation(s)	Solution
Dosing Regimen	Intravenous
Applicant Proposed Indication(s)/Population(s)	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Recommendation on Regulatory Action	Approval
Recommended Indication(s) / Population(s) (if applicable)	Treatment of Amyotrophic Lateral Sclerosis (ALS) / Adults

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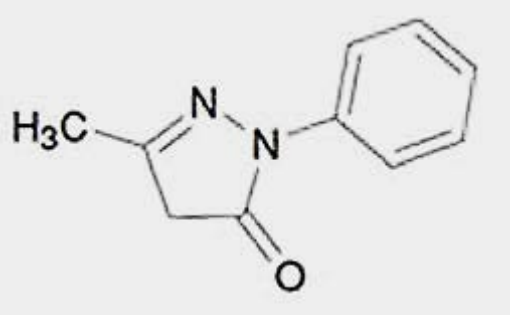
1 Executive Summary

1.1. Product Introduction

Figure 1 Structure of 5-Methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one ("edaravone")



Source: CSR_Protocol:MCI186-19_ver.2.0 p 42/550

- Non-proprietary (or established) name and proposed proprietary name

Established name: Edaravone, Proprietary name: RADICAVA; It is also marketed in India by Edinburgh Pharmaceuticals by the brand name Arone

- The pharmacologic class

Free radical scavenger

- The applicant's proposed dosing regimen(s), route of administration, dosage form, delivery device, and schedule (if applicable)

60 mg administered intravenously over 60 minutes daily for 14 consecutive days followed by a 2-week drug free period (Cycle 1), and then administration of 60 mg administered intravenously over 60 minutes daily for 10 days within a 14 day period followed by a 2-week drug free period (Cycle 2 and thereafter).

- The proposed indication

Treatment of amyotrophic lateral sclerosis (ALS).

- Whether the drug is a new molecular entity (NME)

Yes

1.2. Conclusions on the Substantial Evidence of Effectiveness

This review concludes that there is adequate evidence to recommend an approval of edaravone for the indication of the treatment of Amyotrophic Lateral Sclerosis (ALS). This recommendation is based on a positive single study, MCI186-019 ('Study 19'), and confirmatory evidence from a Phase 2 study, MCI186-016 ('Study 16'). Study 19 conforms to most of the criteria described in the guidance for effectiveness for situations where the presence of one study can contribute to a conclusion that the study would be adequate to support an effectiveness claim. It is a multicenter study with 123 patients randomized 1:1 to active or placebo in the double-blind portion. I felt the design was adequate and well controlled based on the protocol and resulting randomization demographics.

A unique feature of this submission is that all of the Phase 2 and 3 data are from studies conducted in Japanese ALS patients. The applicant has provided an adequate summary supporting the similarity between the data in this program and what one would expect in Caucasians, in terms of:

- Diagnosis of ALS
- Practice of medicine, as it relates to ALS
- Natural history of ALS
- Edaravone pharmacokinetics (PK)
- Edaravone pharmacodynamic effect (efficacy), and Edaravone safety.

The summary of ethnic bridging provides sufficient support use of this data based upon the principles outlined in the ICH Harmonised Tripartite Guideline Ethnic Factors in the Acceptability of Foreign Clinical Data E5 (R1)[1] and the FDAs Guidance for Industry E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data[2]

The primary endpoint in Study 19, the difference between treatment groups in the change from Baseline on the ALSFRS-R analyzed with clinically relevant covariates, was statistically significant with P = 0.0013. The Least Square Mean ± Standard Error (SE) of the difference between the groups ± SE (edaravone group – placebo group) and the 95% confidence interval of this mean was 2.49±0.76 (0.99 to 3.98). Several sensitivity analyses of the primary analysis support this result. Most of the clinically relevant secondary endpoints involving different types of events support the finding with nominal P values of < 0.05 or trending in the right direction ($P < 0.01$). A limitation of this study was that the analysis of the secondary endpoints did not incorporate a means to prevent inflation of alpha.

The supportive study (Study 16) was not positive in its primary analysis although a nominally favorable finding occurred in a post-hoc analysis for a more homogeneous population including

[1] http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E5_R1/Step4/E5_R1__Guideline.pdf
[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073120.pdf

patients with more advanced and more definitive diagnosis (same population analyzed in Study 19). When the population (definite/EESP/2Y) that was to be designated as the Study 19 Full Analysis population was analyzed in Study 16, the difference in treatment arms (EDA – PBO) for the ALSFRS-R was nominally positive in the regression analysis of the change from baseline (3.01±1.33 (0.35, 5.67), P = 0.0270). Repeated measures analysis yielded a similar result (2.20 ±0.76 (0.68, 3.72) P=0.0053. Several of the key secondary endpoints were supportive or trended in the right direction. Limitations of this study include, (1) the post hoc nature of the (definite/EESP/2Y) analysis, (2) analysis of the secondary endpoints did not incorporate a means to prevent inflation of alpha, and (3) imbalances in some of the demographics between treatment arms. Another key limitation of the findings in this study is the apparent lack or possibly negative effect in more advanced patients. Notably, this was the same result in the MCI018 study that was a small Phase 2 study of more advanced patients. In conclusion, I believe Study 16 lends confirmatory evidence to the data from Study 19 to support approval; however, because of the issues described, I do not believe it stands as an independent second study.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Edaravone is thought to be a free radical scavenger with a proposed mechanism of countering oxidative damage hypothesized to occur in the nervous system of patients with ALS.

ALS is a fatal neurodegenerative disease with rapid progression of symptoms that follows the degeneration in motor neurons. Respiratory failure is the leading cause of death in this disorder. It is thought to have different origins (familial versus spontaneous) and initial presentations. Although one year mortality is about typically calculated to be 33%, survival has been described as, 'var[ying] considerably"(Wolf, Safer et al. 2014).

There is one drug approved for ALS, riluzole. The riluzole label notes that measures of muscle strength and neurological function did not show a benefit.

With respect to the evaluation of ***Benefit***, the conclusion of this review is that substantial evidence of clinical efficacy was met in the application. This relies on Study 19 as a single trial with confirmatory evidence from Study 16. These studies show a benefit in patients early in their diagnosis of ALS. This benefit was demonstrated by the fact that patients on drug experienced 2.49 points less decline on the 48-point Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) scale over a 6-month period. This scale measures different functional domains of daily living, as well as patient perception of respiratory insufficiency. Survival was not significantly affected in the studies of this program.

With respect to the ***Risk*** *(including efficacy risks)*, I have 4 principal considerations.

- The safety profile of edaravone, as derived from the ALS development program, does not have any serious safety concerns, however the trials were relatively short and with patients who were at early stages of their disease.
- Postmarketing analysis from other indications revealed about 10 possible cases of hypersensitivity where there was a reasonable chance of causality. Some of the other categories investigated, e.g., thrombocytopenia, had cases although there were confounders or insufficient evidence to attribute causality.
- The duration or persistence of effect is not well characterized, since Study 19 only was controlled for the first 6 cycles.
- Studies 16 and 18 suggest the drug is not effective in more advanced (later than early stage) patients; however, neither of these studies was powered to test that specific question.

I believe what I have heard from patients / patient representatives is that a drug which demonstrates some clinical benefit could have an acceptable risk/benefit profile; even in the face of moderate levels of safety risk or tolerability issues. Evaluation of the ALS database in conjunction with the relatively large postmarketing dataset suggests that the risks are acceptable at this time and that a favorable risk/benefit profile has been presented for RADICAVA for the intended indication. Overall, I believe the Risk/Benefit considerations favor approval with standard postmarketing surveillance and adequate labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ALS is a fatal neurodegenerative disease with rapid progression of symptoms that follows the degeneration in motor neurons. Respiratory failure is the leading cause of death in this disorder. It is thought to have different origins (familial versus spontaneous) and initial presentations. Although one year mortality is about typically calculated to be 33%, but may vary.	ALS is a serious and life threatening disease where a therapy with a true and meaningful treatment effect would be beneficial.
Current Treatment Options	• There is one drug approved for ALS, riluzole. The riluzole label notes that measures of muscle strength and neurological function did not show a benefit.	There is a substantial unmet need for therapies in ALS.
Benefit	• Edaravone seems to have the greatest effect in early stages of ALS; there is no evidence of effect late in disease. The division between early and late stage ALS patients is unclear because of the variability in the disease, so labeling for an early-stage subpopulation in ALS is not feasible. In summary, I recommend approval for labeling of the treatment of ALS	Evidence of effect is based on the primary analysis of Study 19. This benefit was demonstrated by the fact that patients on drug experienced 2.49 points less decline on the 48-point Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) scale over a 6-month period. This scale measures different functional domains of daily living, as well as patient perception of respiratory insufficiency. Survival was not significantly affected in the studies of this program.
Risk	• The trials were of relatively short duration considering the chronicity and variability in this disease. Postmarketing data was generally inconclusive because of cofounders or a lack of specific information in reports.	There were no strong safety signals in the ALS development program. Postmarketing data from other indications suggested a signal for hypersensitivity. Other issues, such as thrombocytopenia and renal failure, cannot be definitively ruled out.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• No strong safety signals are present in the ALS safety database.	I believe based on the evidence in this submission that a standard postmarketing surveillance would be adequate for this drug in the intended population.

2 Therapeutic Context

2.1. Analysis of Condition

Clinical Course ALS is a fatal neurodegenerative disease with rapid progression of symptoms that follows the degeneration in motor neurons. In ALS, the upper (primary) motor neurons and lower (secondary) motor neurons are degenerated and produce progressive dysfunction. Upper motor neuron involvement presents as physical findings such as spasms, tendon hyperreflexia, and pathological reflexes. Lower motor neuron involvement presents as physical findings such as muscular weakness, muscle atrophy, and muscle fasciculation. Impairment of the motor neurons that control the muscles involved in speech and swallowing results in dyslalia and dysphagia, while impairment of the motor neurons that innervate the respiratory muscles results in respiratory signs and symptoms. Eventually, respiratory failure develops as ALS progresses and is a leading cause of death in ALS. Cognitive and behavioral impairment including pseudobulbar affect, sialorrhea, thick mucus, emotional lability, cramps, spasticity, pain, and impaired communication are also signs and symptoms observed in ALS.

In mid- or late-stage ALS, percutaneous endoscopic gastrostomy placement (PEG) is used for nutritional support. Non-invasive respiratory and ventilator support are also used to maintain respiratory function. Tracheostomy may provide additional respiratory support in late stage of ALS, 2 to 3 years from the diagnosis (or 3 to 4 years from the first onset of symptom). About 10% of ALS patients live over 10 years.

Because of the loss of motor function, most patients will need assistance with activities of daily living with subsequent progression leading to respiratory compromise and eventual respiratory failure. Median survival times are consistently reported as 3 years.

Diagnosis and Staging Currently, the ALS diagnostic criteria with the broadest international acceptance are the El Escorial revised Airlie House diagnostic criteria (Motor Neuron Diseases Research Group of the World Federation of Neurology) that were proposed in 1998. In order to diagnose ALS early after onset to encourage clinical research, reliable criteria are necessary at an early stage when the motor neuron system remains mostly intact. The El Escorial revised Airlie House diagnostic criteria grades the certainty of the diagnosis based upon 4 clinical grades as shown below ("Suspected ALS" is deleted from the revised El Escorial Criteria).

- Clinically **"Definite ALS"** is defined on clinical evidence alone by the presence of upper motor neuron (UMN), as well as lower motor neuron (LMN) signs, in the bulbar region and at least 2 spinal regions or the presence of UMN and LMN signs in 3 spinal regions.
- Clinically **"Probable ALS"** is defined on clinical evidence alone by UMN and LMN signs in at least 2 regions with some UMN signs necessarily rostral to (above) the LMN signs.
- Clinically **"Probable ALS Laboratory supported"** is defined when clinical signs of UMN and LMN dysfunction are in only 1 region, or when UMN signs alone are present in 1 region, and LMN signs defined by electromyography criteria are present in at least 2 regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

- Clinically **"Possible ALS"** is defined when clinical signs of UMN and LMN dysfunction are found together in only 1 region or UMN signs are found alone in 2 or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable ALS Laboratory supported cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging, or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

Prevalence In the 2011 census, a total of 12,187 patients were identified with "definite ALS" from October 2010 to December 2011. The overall prevalence rate of ALS was 3.9 per 100,000 and increased as age increased with those aged 18 to 39 years having the lowest prevalence rate (0.5 per 100,000), and the age group 70 to 79 years having the highest prevalence rate (17.0 per 100,000). The ratio of males to females was 1.56. The prevalence rate for Caucasians was 2-fold greater than in African-Americans with Caucasians having a prevalence rate of 4.2 per 100,000 compared with 2.0 per 100,000 for African-Americans.

2.2. Analysis of Current Treatment Options

FDA granted approval for treatment of ALS for riluzole in December 1995. As reported in the riluzole labeling, approval was based upon significance reached for a composite endpoint of time to death or tracheostomy. As noted in the labeling, there was no improvement in survival and the overall difference with placebo was attributable to an increase in the time to tracheotomy or death of 90 days. There was no improvement in muscle strength or neurological function.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

There is no prior US regulatory approval of the active moiety (See Section 3.1.1). The drug is approved and marketed in several countries as described in Section 3.2.

3.1.1. Summary of Presubmission/Submission Regulatory Activity

- 5/12/2015 – Orphan designation for the treatment of ALS.
- 5/13/2015 – IND-126396 received with meeting request (no US trial protocol submission)
- 6/16/15 – Pre-IND meeting to discuss the efficacy findings of Phase III study of edaravone for the treatment of ALS and to obtain on the regulatory pathway needed for approval.3 During the Pre-IND meeting, the Division provided preliminary feedback on the following:
  - Suitability of the proposed NDA data package. *"…Some of your results seem to support your claims, and we believe it would be reasonable for you to submit an NDA. However, our initial impression is that uncertainty remains as to whether, or to what degree, the drug might be effective. Some of our concerns include the number and short duration of trials that may be positive."*

- [redacted] (b) (4) *apparent lack of evidence of efficacy in more advanced patients raises concern that the drug may not be effective in later disease stages, or that efficacy may decrease as disease progresses."*
- Feedback was also provided on a number of required aspects of the proposed NDA submission
- Generalizability of studies conducted in Japan – *"You should clearly address in the NDA the larger issue of whether safety and efficacy results in Japanese ALS patients can be generalized to US patients, based on the data available. We agree this should include evidence supporting your assertion that clinical practice and treatment guidelines related to ALS are similar. You should also directly compare the clinical course of ALS patients in Japan (for example from your placebo arms) to patients at similar disease stage in published US clinical trials."*
- Adequacy of Phase 2 studies with respect to dose exploration – [We]"… *encourage you to study a higher dose because it does not seem that the limit of tolerability has been reached, and higher doses could potentially improve efficacy."*
- Appropriateness for Expedited Programs – "*Given that edaravone is being developed to treat ALS, a serious disease, and because preliminary review of your clinical data suggests that edaravone has the potential to address an unmet need, you may consider applying for fast track status. Breakthrough designation (BTD) requires that you provide preliminary clinical evidence that edaravone demonstrates a substantial improvement on a clinically significant endpoint(s) over available therapies. Importantly, BTD would be based on comparison of edaravone to available therapy, i.e., riluzole. The data that you have submitted suggests that it would be difficult to conclude that the efficacy of edaravone is substantially superior from that of riluzole, and we are skeptical that a more detailed comparison would be productive because of major uncertainty introduced by differences in study population and design.*

  The Division explained that it would consider all available regulatory pathways for approval that might be appropriate, including both full approval and accelerated approval, based on the data submitted."

• 10/22/15, a Pre-NDA CMC to review edaravone's CMC development history and receive guidance prior to submission of the NDA.

• 12/9/15 – Pre-NDA meeting was held. Sponsor presented a plan to establish similarity between the Japanese and US ALS populations and the Division confirmed the plan was acceptable. Indication – The Division recommended something similar to *"...for the treatment of Amyotrophic Lateral Sclerosis." The nature of the effects of the drug will be described further in the Clinical Trials section of labeling if your drug is approved.* [redacted] (b) (4) *you should explain that in your NDA."*

In the meeting discussion, " (b) (4) "

3.2. Foreign Regulatory Actions and Marketing History

Edaravone was first approved in 2001 in Japan, under the trade name of RADICUT®, for the treatment of acute ischemic stroke (AIS) using intravenous (IV) infusion of 30 mg edaravone administered over 30 minutes for up to 14 days of treatment. Edaravone was also approved in Japan in June 2015 and in South Korea in December 2015 for the treatment of ALS based upon a series of clinical studies completed in Japan for ALS. The approved ALS dosing regimen is once a day IV infusion of 60 mg administered over 60 minutes following dosing cycles where Cycle 1 consisted of 14 consecutive treatment days followed by a 2-week drug-free period with all subsequent cycles consisting of 10 treatment days over 2 weeks followed by a 2-week drug-free period.

The applicant conducted 5 Phase I studies in healthy volunteers (3 studies in Japan and 2 studies in Europe (described in Section 9.3.1 of this review)), 8 clinical studies in AIS (6 studies in Japan, 1 study in South Korea, and 1 study in Europe), and 3 clinical studies in SAH in Japan. As a result, approximately 100 healthy patients, 860 AIS patients, and 390 SAH patients were exposed to edaravone (SAH program with slow continuous infusion was terminated due to the lack of efficacy) (Section 5.2). In AIS, a Japanese Phase IIb study investigated 10 mg/30 min, 30 mg/30 min, and 45 mg/30 min of edaravone IV infusion twice a day and, based upon these findings, 30 mg/30 min twice a day (60 mg as daily dose) was selected for the Phase III study of AIS. There was no difference in efficacy between 30 mg/30 min and 45 mg/30 min (Study MCI186-05 CSR). The 30 mg/30 min of edaravone IV infusion twice a day up to 14 days was approved after the positive results from the placebo-controlled Phase III study. Since the approval in 2001, approximately 1.7 million AIS patients have been exposed to edaravone in Japan.

In South Korea, the Sponsor received the orphan designation in February 2015, submitted the NDA in June and the product was approved in South Korea in December 2015 for the following indication of *Delaying Progression of Functional Disorder in Patients With Amyotrophic Lateral Sclerosis*.

Protocol assistance from the Committee for Medicinal Products for Human Use (CHMP) was requested in August 2015 and a letter including advice from CHMP and Committee for Orphan Medicinal Products (COMP) was issued in December 2015.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Proprietary Name Review

Division of Medication Error Prevention and Analysis (DMEPA) Office of Medication Error Prevention and Risk Management (OMEPRM) assessment of RADICAVA did not identify any names that represent a potential source of drug name confusion. Therefore, they maintained that the proposed proprietary name is acceptable from a promotional and safety perspective.

Other reviews were pending at the time of this review's finalization.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

5.2. Sources of Clinical Data and Review Strategy

5.2.1. Table of Clinical Studies

The edaravone clinical development program in ALS started in 2001 after the launch of edaravone for treatment of AIS in Japan. Since the safety profile was based upon the AIS dosing regimen that confirmed the safety of 60 mg/day administered up to 14 days, all dosing in ALS is based upon 14-day administration followed by 2-week drug-free period. The ALS clinical development program consisted of 1 Phase II and 4 Phase III studies (Table 1).

Studies MCI186-16 and -17 enrolled grade 1 and 2 ALS patients (mostly independent in function; See Table 4) while Study MCI186-18 enrolled only grade 3 to explore efficacy and safety of edaravone in more advanced ALS.

Additional exploratory analyses in Study MCI186-16 suggested to the applicant that there was a beneficial effect applicant of edaravone in patients who had functionality retained in most ADL domains with normal respiratory function. Based upon the findings in Study MCI186-16, Study MCI186-19 was prospectively designed to enroll the Definite or Probable/EESP/2y ALS population. This population definition sought to have patients more likely to have ALS (i.e., Definite vs. Probable ALS) and to be at an earlier stage of the disease (e.g., FVC of ≥ 80 versus 70%). The full explanation of this is found in the description of the statistical analysis plan for Study 16 (p. 35)

5.2.1. Review Strategy

In this submission, I consider substantial evidence for efficacy to come from results of the Phase 3 study MCI186-19 with contributory, supportive, confirmatory evidence coming from the analysis of the Phase 2 study MCI186-16. Accordingly, I have conducted a detailed analysis and report of Study 19 and 16 (**Methods**, Section 6; **Results**, Section 7 of this review). Other studies will be summarized in paragraph form at the end of Section 6 of this review.

The primary safety analysis will be from the placebo controlled portion of Studies 16 and 19 (applicant's Group 1; See Section 6.1.2.1 for Population definitions). The Adverse Events table in Section 6 of the drug labeling will be derived from this group. I will evaluate data from all 5 ALS

studies for potential events emerging after extended treatment and for rare or idiosyncratic events (e.g., potentially, certain types of hypersensitivity). Deaths and SAEs from postmarketing data (See Section 8.5 for information on postmarketing data from foreign approvals) will be reviewed for trends and significant events.

Table 1 Studies in the ALS Development Program

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

[a] Classified according to the Japan ALS severity classification (refer to Section 2.7.4.3.1.4 for a description of this grading scale).
[b] Double-blind phase
[c] Active phase.
P group: placebo group
E group: edaravone group
EP group: edaravone group in MCI186-16 followed by placebo group in MCI186-17
EE group: edaravone group in MCI186-16 followed by edaravone group in MCI186-17
PE group: placebo group in MCI186-16 followed by edaravone group in MCI186-17
P-E group: placebo group in double-blind phase of MCI186-19 followed by edaravone group in active phase of MCI186-19
E-E group: edaravone group in double-blind phase of MCI186-19 followed by edaravone group in active phase of MCI186-19
Source: CSRs for MCI186-12, MCI186-16, MCI186-17, MCI186-18, and MCI186-19.

Source: Module 5.2

6 Review of Relevant Individual Trials for Efficacy

Section 6.1 will present a detailed report on the methodology of Studies 19 and 16. A brief narrative description will follow in this section for Studies 12, 17, and 18. A detailed description of results for Studies 19 and 16 will follow in Section 6.2. Relevant data from the controlled portion of Study 17 and from Study 18 will follow this and relevant uncontrolled pharmacodynamic data from Studies 12 and 17.

Table 2 presents a summary of the key design features of the 5 studies.

Table 2 Key Clinical Studies Design Features

	MCI186-12 (FAS)	MCI186-16 (FAS)	MCI186-16 (EESP)[a]	MCI186-16 (Definite or Probable/EESP/2y)[b]	MCI186-17	MCI186-18 (FAS)	MCI186-19 (FAS)
El Escorial and revised Airlie House diagnostic criteria	Not prespecified	Definite Probable Probable-laboratory-supported	Definite Probable Probable-laboratory-supported	Definite Probable	Patients who completed Study MCI186-16 (FAS, EESP, Definite or Probable /EESP/2y)	Definite Probable Probable-laboratory-supported	Definite Probable
ALS severity classification	Not prespecified	Grade 1 Grade 2				Grade 3	Grade 1 Grade 2
ALSFRS-R score at Baseline	Not prespecified	Not prespecified	≥2 points on each individual items			Not prespecified	≥2 points on each individual items
Change in ALSFRS-R score during 12-wk pre-observation period	Not prespecified	Changed by -1 to -4 points				Changed by -1 to -4 points	Changed by -1 to -4 points
Respiratory function (%FVC)	Not prespecified	%FVC ≥70%	%FVC ≥80%			%FVC ≥60%	%FVC ≥80%
Respiratory function (other criteria)	Without impaired respiratory function (complaining respiratory discomfort)[c]	4 points on items of Dyspnea, Orthopnea, and Respiratory insufficiency in ALSFRS-R score				4 points on items of Dyspnea, Orthopnea, and Respiratory insufficiency in ALSFRS-R score	4 points on items of Dyspnea, Orthopnea, and Respiratory insufficiency in ALSFRS-R score
Onset of ALS	Not prespecified	Within 3 years		Within 2 years		Within 3 years	Within 2 years

a EESP: patients with "2 points or better, on each of the individual items of the ALSFRS-R" and "%FVC greater than or equal to 80%" in the FAS. EESP was set in an additional exploratory analysis of Study MCI186-16, and was specified before the code break of Study MCI186-17.
b Definite or Probable/EESP/2y: patients with "definite or probable diagnostic criteria for ALS" and "within 2 years after the onset of ALS" in the EESP.
c Patients who underwent a tracheotomy or were using a ventilator were excluded.
Source: MCI186-12, -16, -17, -18, and -19 CSRs.

6.1. Study Design

6.1.1. Study MCI186-19

Overview and Objective

Trial Design

- ***General Design Characteristics***

This was a multicenter, double-blind, placebo-controlled parallel-group study conducted from August 2011 to March 2015. The trial had 3 periods:

- Pre-observation period: A 12-week observation period was set prior to the start of Cycle 1.
- Cycle 1: Treatment for 14 consecutive days, followed by a drug-free period of 2 weeks.
- Cycles 2 to 12: Treatment for 10 days per 2 weeks, followed by drug-free period of 2 weeks

Table 3 MCI186-19 Schedule of Events

		Eligibility check	Pre-registration	Pre-observation period	Registration	Treatment period										At Discontinuation
						Double-blind period						Active treatment period (for patients wishing to participate)				
						Cycle 1		Cycles 2 to 5		Cycle 6		Cycles 7 to 11		Cycle 12		
						Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	
						14 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	
Informed consent		⊙														
Patient characteristics	Patient demographic characteristics	●		●												
	Body weight	●		●				←	→	←	→	←	→	←	→	
	Complications, current medical history	●		●												
	Concomitant medication, concomitant therapy	●	←	←	←	←	←	←	←	←	←	←	←	←	→	●
Registration			Δ		Δ											
Efficacy	ALSFRS-R	●	←	12 Weeks ●	→		●		●		●		●		●	●
	%FVC	●		●			●		●		●		●		●	●
	Modified Norris Scale			●							●				●	●
	ALSAQ40			●							●				●	●
	Grip strength, pinch grip strength			●			●		●		●		●		●	●
	Japan ALS severity classification	●		●							●				●	●
	Death or certain disease progression*					←	←	←	←	←	←	←	←	←	→	○ (2 weeks after the last dose)
Safety	Clinical laboratory tests	●		●[1]	●[2]	●[3]●[4]●		●		●	●	***●		●	●	●
	Sensory tests				●[2]	●		●		●	●	●		●	●	●
	(Blood gases)**						○		○		○		○		○	○
	Adverse events*					←	←	←	←	←	←	←	←	←	→	○ (2 weeks after the last dose)
Blood sampling for genetic analysis study[Note]						←	←	←	←	←	←	←	←	←	→	

Clinical laboratory tests (measured at a central laboratory) ●1: Performed between 28 days before registration and the day before registration, ●2: Performed before administration, ●3: Performed on Day 3 of Cycle 1, ●4: Performed on Day 7 of Cycle 1

*The occurrence of death or certain disease progression and adverse events was examined from the start of Cycle 1 to 2 weeks after the last dose. The examinations were performed through 4 weeks after the end of treatment by means such as patient interviews.

: Blood gases were measured if %FVC was ≤50%. *: In Cycle 7, performed on Day 3 and Day 7 and the day of administration completion. [Note]: Blood collected once between registration and the end of Cycle 12 or at discontinuation in patients who consented to blood sampling for the genetic analysis study.

Source: CSR Table 9.5.1.1-1, p. 53/550

- ***Population***

  – *Diagnostic criteria*

Patients with ALS (according to the El Escorial revised Airlie House diagnostic criteria)

  – *Key inclusion/exclusion criteria (not original I/E numbering)*

Inclusion

(1) Patients who are categorized as either "Definite ALS" or "Probable ALS" in the El Escorial revised Airlie House diagnostic criteria
(2) Patients at Grade 1 or 2 in the Japan ALS severity classification
(3) Patients scoring ≥2 points on each single ALSFRS-R item ("4. Handwriting" and "5. Eating motion (1)" should be scored ≥2 points on each side.)
(4) Patients with normal respiratory function (%FVC is ≥80%; to be assessed using the actual values.)
(5) Patients with ALS that occurred within 2 years at the time of providing written informed consent
(6) Patients aged 20 to 75 years at the time of providing written informed consent
(8) Patients in who change in ALSFRS-R score during the 12-week pre-observation are -1 to -4 points.

Exclusion
(1) Patients with decreased respiratory function and a complaint of dyspnea at registration
(2) ≤3 points on any of the following 3 ALSFRS-R items: "10. Respiration (1) dyspnea, (2) orthopnea,(3) respiratory insufficiency")
(3) Patients with the possibility that the current symptoms may be symptoms of a disease requiring differential diagnosis, such as cervical spondylosis and multifocal motor neuropathy
(4) Patients previously administered edaravone
(5) Patients with renal impairment indicated by creatinine clearance (Ccr) ≤50 mL/min between 28 days before the date of registration and the registration date (Ccr value calculated from serum creatinine level).

- ***Treatments***

  – *Study treatments*

    - Edaravone 60 mg or edaravone placebo (2 ampules per administration) was diluted with saline at the time of use and administered once daily over 60 min

  – *Regimen*

    - Cycles 1 to 6: edaravone at 60 mg/day, placebo; Cycles 7 to 12: edaravone at 60 mg/day. Cycles had a window of ± 3 days

- *Dose selection*
  - The daily dose and mode of administration were the same as the dosage and administration used in the previous studies.
- *Assignment to treatment*
  - The company used a dynamic allocation of patients to the edaravone and placebo groups at a proportion of 1:1 based on the following 3 factors.
    - Change (difference, -1, -2/-3, -4) in the ALSFRS-R score between baseline in the pre-observation period and completion of the pre-observation period (12 weeks)
    - El Escorial revised Airlie House diagnostic criteria (definite/probable), and
    - Age (≥65/<65 years)
- *Concurrent medications:*
  - Use of a riluzole preparation was permitted from the day of the ALSFRS-R evaluation before pre-registration until the end of Cycle 12 (or discontinuation) if the dosage and administration were not changed. Dose reduction, dose interruption, or discontinuation in response to an adverse event, dysphagia progression, or gastrostomy was permitted. It is prohibited to newly start the use of riluzole preparations except for dose increase after dose reduction or resumption after dose interruption. However, initiating treatment with a riluzole preparation for the first time was prohibited.

- ***Subject completion, discontinuation, or withdrawal:***

- *Discontinuation Criteria*
  - The patient requested discontinuation.
  - The patient was found to be clearly ineligible for the study.
  - The investigator (or subinvestigator) decided it difficult to continue the patient's participation in the study due to an adverse event
  - Tracheotomy was required.
  - Respiratory support was required all day long.
  - The investigator (or subinvestigator) decided it inappropriate to continue the patient's participation in the study due to worsening of the primary disease.
  - The patient underwent spinal surgery for cervical spondylosis, intervertebral disc hernia, etc.
  - The patient showed %FVC≤50%, and PaCO2 (blood gas)> 45 mmHg. The patient's participation in the study was immediately terminated if %FVC was ≤50% and blood gas PaCO2 ≥45 mmHg. The decision was made using the actual examination values. The patient's participation in the study was to be terminated if PaCO2was ≥45 mmHg even if the timing of the blood gas measurement was outside the acceptable range. The need for discontinuation was considered if %FVC was ≤50% or PaCO2 ≥45 mmHg and signs of respiratory muscle dysfunction were seen.
  - The patient showed the creatinine clearance of ≤50 mL/min. (Ccr calculated from the serum creatinine level). The need for discontinuation was considered even if the Ccr value was greater than 50 mL/min but signs of acute renal failure were seen, such as a rapid decrease in the test value.

- Other cases where the investigator (or subinvestigator) decided that the patient's participation in the study should be terminated.

- ***Study Endpoints***

1. ALSFRS-R

The ALSFRS-R scale is a twelve question evaluation of ALS patients' fine motor, gross motor, bulbar, and respiratory function. Each question has five possible responses, with normal function worth 4 points and the greatest degree of impairment scoring 0 points.

Rater training was provided before the start of the study using a video that demonstrated the evaluation method.

2. %FVC

A %FVC is justified as important in the present trial because "Method for the Evaluation of Respiratory Function in ALS" in the ALS Treatment Guideline 2002 lists a decrease in %FVC (not higher than 50%) as a criterion for respiratory support and that it is significant to delay the need to live with respiratory support.

3. Modified Norris Scale

The Modified Norris Scale is a rating scale for the evaluation of physical function in amyotrophic lateral sclerosis (see **Appendix 1. Norris Scal**e)

4. ALSAQ40

The questionnaire consists of 40 statements about difficulties that you may have experienced during the prior 2 weeks on a scale from Never/Rarely/Sometimes/Often/Always (or can't do function).

Medical reviewer's comments and analyses – The test contains both functional (*"I have found picking things up difficult."*) *and perceptual ("I have felt self-conscious* [sic] *about my speech.") items. The questionnaire also contains items that seem on face to be functional but that could be multifactorial with respect to the etiology of the perceived deficiency* ("*I have talked less than I used to.*"). Because of the sub-optimal construct of this questionnaire, I did not include it in my analysis of the NDA, but did inspect each items scoring to see if there were any notable trends in the data.

5. Grip strength, pinch grip strength

Pinch grip strength was measured by a method in which the pad of the thumb was placed in opposition to the lateral aspect of the index finger (lateral pinch). The measurement value and date were recorded on the case report form. The units used were kilograms, and the values were read to 1 decimal place. If a measurement could not be performed, that was indicated on the case report form.

6. Japan ALS severity classification

Table 4 Japanese ALS Severity Scale

Grade 1:	Able to work or perform housework;
Grade 2:	Independent living but unable to work;
Grade 3:	Requiring assistance for eating, excretion, or ambulation;
Grade 4:	Presence of respiratory insufficiency, difficulty in coughing out sputum, or dysphagia;
Grade 5:	Using a tracheostomy tube, tube feeding, or tracheostomy positive-pressure ventilation.

Source: MCI186-19-Protocol, Section 16.1.1, p. 250/267

7. Death or certain disease progression
    a. In the case of discontinuation, 2 weeks after the last dose.
    b. tracheotomy, which was established as a discontinuation criterion,
    - Event description
    - Death
    - Disability of independent ambulation: Rating of 0 points ("No purposeful leg movement") for ALSFRS-R item "8. Walking" was used as criterion.
    - Loss of upper limbs function: Criterion was ALSFRS-R rating of 0 points for all of the following items: "4. Handwriting," "5. Eating motion," and "6. Dressing and hygiene" (i.e., "4. Handwriting" ["Unable to grip pen"]; "5. Eating motion (1): Handling utensils (patients without gastrostomy)" ["Needs to be fed"]; "5. Eating motion (2): Finger motion (patients with gastrostomy)" ["Unable to perform any aspect of task"]; and "6. Dressing and hygiene" ["Total dependence"]).
    - Tracheotomy
    - Use of respirator: Did not include the use of BiPAP.
    - Use of tube feeding: Criterion was ALSFRS-R rating of 0 points for "3. Swallowing" ("NPO (Exclusively parenteral or enteral feeding)").
    - Loss of useful speech: Criterion was ALSFRS-R rating of 0 points for "1. Speech" (Loss of useful speech).

- ***Statistical Analysis Plan***

Populations Proposed for Analysis
(1)Full Analysis Set (FAS)
The FAS is an analysis set consisting of all patients except the following patients:
- Patients who have been found to have no ALS
- Patients who have never received investigational product
- Patients with no efficacy data after treatment with the investigational products
(2) Per Protocol Set (PPS)
The PPS is an analysis set consisting of all patients in the FAS except the following patients:

- Patients who deviate from the inclusion criteria
- Patients who have violated the exclusion criteria
- Patients who have violated the rules for prohibited concomitant drugs
- Patients with a frequency of infusion of the investigational products of not higher than 70% of the frequency defined in the protocol.

3.2 Safety Analysis Set (SAS)

The safety analysis set is an analysis set consisting of all patients except the following patients:
- Patients who have never received investigational product
- Patients with no safety data after treatment with the investigational products

5.3.1 Primary Endpoint

ALSFRS-R score change from "baseline in Cycle 1" to "the end of Cycle 6 or discontinuation" was analyzed by using the factors in a dynamic allocation as covariates to perform treatment group comparisons. For patients whose data at "the end of Cycle 6" are missing, data was imputed by the last observation carried forward (LOCF).

5.3.1.2 Secondary Analyses

A repeated measurements analysis of variance was performed by using treatment groups, time points, and the interaction between treatment group and time point as factors and "baseline in Cycle 1," and factors used for dynamic allocation as covariates, for comparison difference between the treatment groups. Analysis was performed in consideration of the time-dependent changes using the statistical model such as mixed effect model. A survival analysis was performed using events defined according to ALSFRS-R score.

In order to investigate time to death or certain disease progression, death, disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding and loss of useful speech will be defined as events, and survival analysis will be performed %FVC, Modified Norris Scale score, ALSAQ40 score, grip strength, and pinch grip strength was analyzed in the same method of ALSFRS-R score.

6.5.2.5 Multiple Comparison/Multiplicity

No correction for multiple comparisons was described in the protocol or Statistical Analysis Plan (SAP). According to the protocol, *"…There is no multiplicity problem because tests will not be performed in evaluation during the active treatment period."*

6.5.2.3 Interim Analyses and Data Monitoring

Not applicable in this study.

Medical Officer's Comments: The lack of a planned hierarchy or plan for controlling for inflation of alpha for testing secondary endpoints is concerning and prevents one from fully considering even some of the positive findings from the study for inclusion in labeling. I do believe though, that on face, positive results on these endpoints may support the finding of efficacy, just as negative secondaries would detract from the support.

Protocol Amendments

Protocol amendments (Section 9.8 of the CSR) were evaluated for potential to change the outcome of analysis. I was not concerned with any of the amendments reported by the applicant.

6.1.2. Study MCI186-16

While described second in this review because of the relative importance in contribution to the evidence for approval, it is important to note that Study 16 was done before Study 19. The post hoc results from Study 16 were used to define the Study 19 full analysis population.

6.1.2.1. Study Design

Overview and Objective

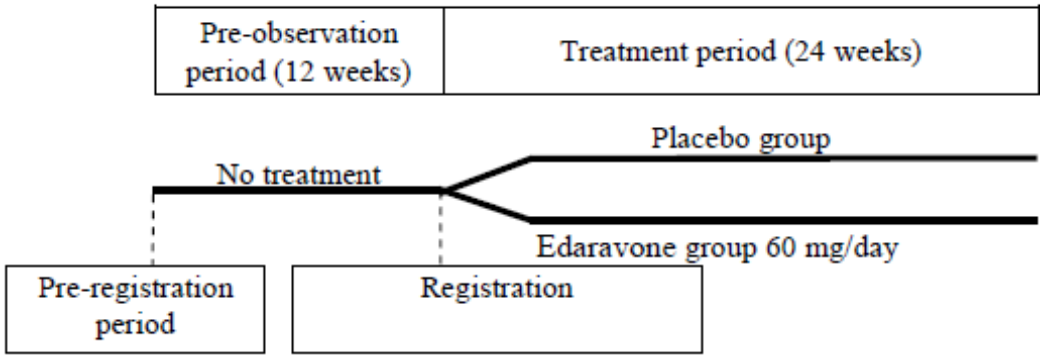
A double-blind, parallel group comparative study was conducted to evaluate the efficacy of edaravone at a once daily dose of 60 mg in comparison with edaravone placebo in patients with amyotrophic lateral sclerosis (ALS) for changes in Revised ALS Functional Rating Scale (ALSFRS-R) over 24 weeks after treatment initiation (Figure 2).

Trial Design

- ***General Design Characteristics***

This was a multicenter, placebo-controlled, double-blind, parallel-group comparative study (Table 5). After completion of the confirmatory study, patients who gave informed consent to participation in an extension study were continuously treated with the investigational product for the extension study.

Figure 2 Schematic Diagram of Study -016



Source: MCI186-16 CSR, Fig. 9.1.6.1, p. 38/772

Table 5 Schedule of Events for Study MCI-016

Table 9.5.1.1-1 Observations, tests, investigation items and investigation schedule

		Eligibility check	Pre-registration	Pre-observation period	Registration	Treatment period of the investigational product												At discontinuation
						Treatment cycle 1		Treatment cycle 2		Treatment cycle 3		Treatment cycle 4		Treatment cycle 5		Treatment cycle 6		
						Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	
						14 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	
Informed consent		⊙																
Patient background	Patient background	•		•														
	Body weight	•		•				←	→	←	→	←	→	←	→	←	→	
	Complications and present illness	•		•														
	Concomitant drugs and therapies	•	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	•
Registration			△		△													
Efficacy	ALSFRS-R	← •	=	= = = → 12 weeks •			•		•		•		•		•		•	•
	%FVC	•		•			•		•		•		•		•		•	•
	Modified Norris Scale			•													•	•
	ALSAQ40			•													•	•
	Grip strength and pinch grip strength			•			•		•		•		•		•		•	•
	ALS severity classification	•		•													•	•
	Death or certain disease progression*					←	←	←	←	←	←	←	←	←	←	←	←	○ (2 weeks after the last dose)
Safety	Laboratory test	•		•[1]	•[2]	•[3]•[4]•		•[5] •		•[5] •		•[5] •		•[5] •		•[5] •	•	•
	Sensory test				•[2]	•		•		•		•		•		•	•	•
	Adverse events*					←	←	←	←	←	←	←	←	←	←	←	←	○ (2 weeks after the last dose)

Laboratory tests (central measurement)

•[1]: Performed between 28 days and the day before registration for the treatment period; •[2]: Before treatment of Day 1 of Treatment cycle 1; •[3]: Day 3 of Treatment cycle 1; •[4]: Day 7 of Treatment cycle 1; •[5]: Day 5 of Treatment cycles 2 to 6

*: Death or certain disease progression and AEs were monitored from treatment initiation in Treatment cycle 1 to 2 weeks after the last dose and to before treatment in the extension study. These endpoints were investigated by, e.g., interview before 4 weeks after treatment completion.

- ***Population***

  – *Key Inclusion/Exclusion Criteria*

Inclusion
[At pre-registration]
(1) Patients who correspond to "definite ALS," "probable ALS," or "probable ALS-laboratory supported" by the El Escorial revised Airlie House diagnostic criteria
(2) Patients with ALS severity grade 1 or 2 by the ALS severity classification
(3) Patients whose % forced vital capacity (%FVC) is 70% or higher
(4) Patients who are within 3 years after the onset of ALS at written informed consent
[At registration]
(7) Patients whose ALSFRS-R score have changed by –1 to –4 points during the 12-week pre-observation period

Exclusion
(1) Patients who complain of dyspnea with deteriorated respiratory function at registration (the ALSFRS-R score is 3 points or lower for any of the 3 items "(1) Dyspnea, (2) Orthopnea and (3) Respiratory insufficiency in 10. Respiration")
(9) Patients with renal impairment based on creatinine clearance (Ccr) of 50 mL/min or lower between 28 days and the day before registration (calculate the Ccr from serum creatinine data)

- ***Treatment***

  – *Test drug*

Edaravone Injection 30 mg: An injection containing 30 mg of edaravone per 20-mL ampule

  – *Control drug*

Edaravone Injection Placebo: A placebo injection whose appearance is indistinguishable from edaravone Injection 30 mg

  – *Regimen*

Pre-observation period: A 12-week observation period before the start of Cycle 1 is designed.
Cycle 1: The investigational product administered for 14 consecutive days, followed by a 2-week drug free period.
Cycles 2 to 6: The investigational product administered for a total of 10 days per 2 weeks, followed by a 2-week drug free period after the end of each Cycle.

Each treatment cycle consisted of treatment and drug free periods, and this treatment cycle was repeated 6 times (approximately 24 weeks). Patients could be treated on both an inpatient and outpatient basis in each treatment cycle.

Table 6 Treatment Regimen for Study -016

Informed consent	Eligibility check	Pre-registration	12-week pre-observation period	Registration	Treatment period											
					Treatment cycle 1		Treatment cycle 2		Treatment cycle 3		Treatment cycle 4		Treatment cycle 5		Treatment cycle 6	
					Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free	Treatment	Drug-free
					14 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days	10 days (/14 days)	14 days

Source: MCI186-16 CSR, Fig. 9.1.4.1, p. 44/772

– *Concomitant medications*

(1) Restricted concomitant drugs: Permitted to use riluzole without changes in the dosage and administration between the day of evaluation of ALSFRS-R score before pre-registration and the end of Cycle 6, and until before treatment in the extension study or at discontinuation. It will be allowed to reduce, suspend, or discontinue the dose of riluzole at the onset of AEs or aggravation of dysphagia. Initiation of riluzole therapy will be prohibited in all patients except those in whom treatment is suspended.
(2) Prohibited concomitant drugs: It will be prohibited to use any drug whose efficacy has been reported in ALS patients, other investigational drugs, and edaravone [*sic*; this is as the protocol appears, although this statement seems to be in error] between the day of ALSFRS-R score before pre-registration and the end of Cycle 6, and until before treatment in the extension study or at discontinuation. Other treatments will be permitted.

– *Randomization*

The study drug assignment manager allocated investigational products for 420 patients in a block of 4 patients (in serial numbers) at a ratio of 1:1 between the edaravone and placebo groups. The dynamic allocation procedure was used by the minimization method with the following 3 factors that were considered to affect drug efficacy evaluation.
• Factor 1: "ALSFRS-R score changes from the start to the end (12 weeks later) of the pre-observation period)"; Two levels (-1, -2/-3, -4)
• Factor 2: "Initial symptom"; two levels (bulbar symptoms/limb symptoms)
• Factor 3: "Concomitant use of riluzole"; Two levels (Yes or No)

- ***Study Endpoints***

Study endpoints were the same as those in Study MCI-19

Statistical Analysis Plan

- ***Populations***

FAS and PPS populations were defined as Study -019

- ***Primary efficacy endpoint:*** ALSFRS-R

Summary statistics (mean, standard deviation, minimum, median, maximum) of the ALSFRS-R score, the primary endpoint, was calculated by treatment group for each time point. Summary statistics will be also calculated for changes in the AFSRS-R score from "baseline in Cycle 1."

– *(a) Primary analysis*

According to the applicant, *"...it will be regarded that the efficacy of edaravone is confirmed when there is a significant difference between the edaravone and placebo groups in any of the following analyses (i) and (ii). The 95% confidence interval (C.I.) of the between-group difference will be calculated only as a guide for interpretation of analysis results.*
(i) Changes from "baseline in Cycle 1" to "the end of Cycle 6 (or at discontinuation)" will be analyzed using the factors employed in dynamic allocation as covariates, and the results of analysis of covariance will be compared between the treatment groups. In patients whose data are missing at "the end of Cycle 6," the data will be imputed by the method of the Last Observation Carried Forward (LOCF).
(ii) For the ALSFRS-R score by time point, the repeated measures analysis of variance will be performed using treatment, time, and the treatment-by-time interaction as factors and "baseline in Cycle 1" and dynamic allocation factors as covariates and the analysis results will be compared between the treatment groups."

– *Sample Size*

Formal sample size was not calculated for this study. The following was extracted from the protocol, *"…It is considered, based on phase II study results, that the upper limit of the target sample size would be 100 patients per group in view of the feasibility of a phase III study."*

- ***Subject Discontinuation Rules***

  - **Criteria for Study Discontinuation**
    - When the patient requested study discontinuation
    - When the patient experienced an AE and it was assessed difficult to continue the study
    - When the patient underwent tracheotomy due to worsening of the underlying condition
    - When the patient was found to be pregnant
    - When protocol deviation was unavoidable and was assessed difficult to continue study
    - When the Ccr became higher than 50 mL/min
    - When the patient turned out to be ineligible as a study patient after study initiation
    - When it turned out impossible to continue the study for the sake of patient's convenience
    - When the investigator or subinvestigator assessed it difficult to continue the study due to reasons other than the above Note) the investigator or subinvestigator was to assess whether the study should be discontinued in patients with such signs of acute renal failure as acute Ccr reduction even when the Ccr was higher than 50 mL/min.

- ***Protocol Amendments***

Protocol Amendments were evaluated (Section 16.1.1.2) and determined not likely to have

affected the outcome or analysis. Post-hoc changes in analysis are discussed in the Section below.

- ***Post-Hoc Analyses***

The additional analysis was performed in the EESP, defined below, after code breaking. The applicant had prior consultation on January 14, 2011 with the PMDA based on the results of additional analysis. The PMDA advised as follows: *"The result of additional analyses showing that edaravone is shown to be effective in patients with mild ALS is reasonable. The results of the additional analyses do not ensure application and approval."*

1) Efficacy Expected Subpopulation (EESP)
All patients excluding the following patients from the FAS with…
- any parameters of ALSFRS-R score of ≤ 1 point at baseline in Treatment cycle 1
- %FVC of < 80% at baseline in Treatment cycle 1
2) Definite or probable ALS and EESP and within 2 years (definite/EESP/2Y)
All patients in the EESP excluding those…- who did not meet "definite or probable ALS" criteria according to the El Escorial revised Airlie House diagnostic criteria

6.2. **Study Results**

6.2.1. **MCI186-19**

Patient Disposition

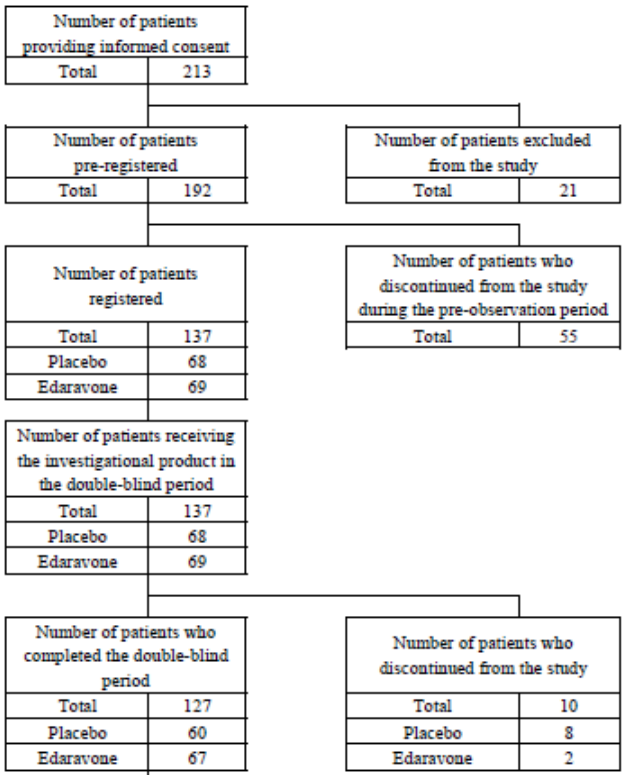
137 patients were randomized, 68 to PBO and 69 to EDA; of these all received treatment. Eight (8) patients in the PBO arm and 2 in the EDA arm discontinued the study. Reasons for discontinuation are found in Table 7. No pattern of concern is noted in the discontinuations.

Table 7 Detailed Reasons for Discontinuation (Study 19 FAS)

Group	Placebo		Edaravone	
No. of patients	68		69	
Reasons for discontinuation	No. of patients	(%)	No. of patients	(%)
1: The patient requested discontinuation.	2	(2.9)	0	(0.0)
2: The patient was found to be clearly ineligible for the study.	0	(0.0)	0	(0.0)
3: The investigator (or subinvestigator) decided it difficult to continue the patient's participation in the study due to an adverse event, etc.	2	(2.9)	0	(0.0)
4: Tracheotomy was needed.	1	(1.5)	1	(1.4)
5: Respiratory support was needed all day long.	1	(1.5)	0	(0.0)
6: The investigator (or subinvestigator) decided it inappropriate to continue the patient's participation in the study due to worsening of the primary disease.	0	(0.0)	0	(0.0)
7: The patient underwent spinal surgery for cervical spondylosis, intervertebral disc hernia, etc.	0	(0.0)	0	(0.0)
8: The patient showed %FVC of ≤50% and $PaCO_2$ (blood gas) of ≥45 mmHg.	1	(1.5)	1	(1.4)
9: The patient showed the creatinine clearance of ≤50 mL/min.	0	(0.0)	0	(0.0)
10: Other cases where the investigator (or subinvestigator) decided that the patient's participation in the study should be terminated.	1	(1.5)	0	(0.0)

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 10.1.1-3, p.89/550

Figure 3 Disposition of Patients in Study 19, Double Blind Phase



Source: CSR_Protocol:MCI186-19_ver.2.0, Figure 10.1.2-1

Protocol Violations/Deviations

Violations/Deviations were further evaluated with the listings in Appendix 16.2.2.1 Protocol Deviations (double-blind period) from the Study report. Of note, were missing data at discontinuation for several key assessments for Subjects 068, 153, 162, 188, 239, all Placebo treated patients.

Table 8 Deviations during the Double Blind Period of Study 19

Deviation Criteria	N EDA	N PBO
a: Patient who was enrolled in the study despite not meeting the inclusion criteria.	0	0
b: Patient who met a discontinuation criterion during the study period but the treatment was not discontinued	0	0
c: Patient for whom treatment method or dose was inappropriate	8	5
d: Patient who received a prohibited concomitant therapy	1	0
e: Patient who had missing values for some endpoints (including test parameters) or for whom the time of the evaluation was outside the acceptable range	4	8
Other (5/3 ICF-related; 1/0 Missing source data; 0/1 untrained investigator assessment)	10	12

Source: Information extracted from CSR_Protocol:MCI186-19_ver.2.0, Table 10.2.1-1 pp. 88-9/550

Table 9 contains patients excluded from the efficacy set and reasons.

Table 9 Number of patients excluded from efficacy analysis set and reasons for exclusion

Patients excluded (in accordance with protocol)	Patient data included/excluded		No. of patients	
	FAS	PPS	Placebo	Edaravone
Patients without ALS	×	×	0	0
Patients not administered the investigational product	×	×	0	0
Patients with no efficacy data after treatment with the investigational product	×	×	0	0
Patients who did not meet the inclusion criteria	○	×	0	0
Patients who met an exclusion criterion	○	×	0	0
Patients with violations of the provision on prohibited concomitant drugs	○	×	0	0
Patients who received ≤70% of the number of investigational product doses prescribed in the protocol	○	×	5	1
Patients whose ALSFRS-R was evaluated by an untrained rater	×	×	0	1*

Population analyzed: patients who were registered in the double-blind period
○: Included, ×: Excluded
*Excluded only for the relevant cycle (Cycle 2).

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.1.1-1, p. 94/550

Medical Officer's Comments: In general, the quality of the data was adequate for review.

Demographics

Demographics were well balanced between the treatment arms in Study 19. Notable observations include:

- Most (>90%) subjects were taking riluzole.
- The large percentage of subjects having a baseline ALSFRS being > 40, Japanese ALS Severity Score in categories 1 or 2, and brief disease duration (~one year) suggests this is a population with relatively early ALS relative to other published clinical trials.
- The high percentage of subjects with Definite or Probable ALS according to the diagnostic criteria lends face validity to the results being applicable to the target population.

Table 10 Demographic and other baseline characteristics in Study 19 (FAS Population)

Treatment group		Placebo		Edaravone		Statistical test
No. of patients		68		69		
Variable		No. of patients	(%)	No. of patients	(%)	
Sex	Male	41	(60.3)	38	(55.1)	*P*=0.6051 (Fisher)
	Female	27	(39.7)	31	(44.9)	
Age* (yrs)	No. of patients	68		69		*P*=0.8111 (Two-sample *t*-test)
	Mean	60.1		60.5		
	SD	9.6		10.1		
	Minimum	38		30		
	Median	61.5		62.0		
	Maximum	75		75		
	<20	0	(0.0)	0	(0.0)	*P*=0.9837 (Two-sample Wilcoxon test)
	≥20, <30	0	(0.0)	0	(0.0)	
	≥30, <40	2	(2.9)	5	(7.2)	
	≥40, <50	7	(10.3)	5	(7.2)	
	≥50, <60	18	(26.5)	16	(23.2)	
	≥60, <70	29	(42.6)	31	(44.9)	
	≤70	12	(17.6)	12	(17.4)	
	<65	46	(67.6)	46	(66.7)	*P*=1.0000 (Fisher)
	≥65	22	(32.4)	23	(33.3)	
Disease duration (yrs)	No. of patients	68		69		*P*=0.3980 (Two-sample *t*-test)
	Mean	1.06		1.13		
	SD	0.47		0.46		
	Minimum	0.2		0.3		
	Median	1.00		1.00		
	Maximum	1.9		2.0		
	<1	33	(48.5)	27	(39.1)	*P*=0.3037 (Fisher)
	≥1	35	(51.5)	42	(60.9)	
Initial symptom	Bulbar symptom	14	(20.6)	16	(23.2)	*P*=0.8368 (Fisher)
	Limb symptom	54	(79.4)	53	(76.8)	
ALS diagnosis	Sporadic	66	(97.1)	68	(98.6)	*P*=0.6195 (Fisher)
	Familial	2	(2.9)	1	(1.4)	

Treatment group		Placebo		Edaravone		Statistical test
No. of patients		68		69		
Variable		No. of patients	(%)	No. of patients	(%)	
El Escorial revised Airlie House diagnostic criteria*	Definite ALS	27	(39.7)	28	(40.6)	*P*=1.0000 (Fisher)
	Probable ALS	41	(60.3)	41	(59.4)	
Japan ALS severity classification	Grade1	16	(23.5)	22	(31.9)	*P*=0.3408 (Fisher)
	Grade 2	52	(76.5)	47	(68.1)	
Complications	Absent	6	(8.8)	4	(5.8)	*P*=0.5316 (Fisher)
	Present	62	(91.2)	65	(94.2)	
Pre-observation period ALSFRS-R score: Before pre-registration	No. of patients	68		69		*P*=0.8331 (Two-sample *t*-test)
	Mean	43.5		43.6		
	SD	2.2		2.2		
	Minimum	39		38		
	Median	44.0		44.0		
	Maximum	48		48		
Pre-observation period ALSFRS-R score: At baseline in Cycle 1	No. of patients	68		69		*P*=0.8225 (Two-sample *t*-test)
	Mean	41.8		41.9		
	SD	2.2		2.4		
	Minimum	37		36		
	Median	42.0		42.0		
	Maximum	47		47		
Pre-observation period ALSFRS-R score: Change from before pre-registration to Cycle 1 baseline*	-4	3	(4.4)	5	(7.2)	*P*=0.7226 (two-sample Wilcoxon test)
	-3	8	(11.8)	7	(10.1)	
	-2	25	(36.8)	21	(30.4)	
	-1	32	(47.1)	36	(52.2)	
	-4, -3	11	(16.2)	12	(17.4)	*P*=1.0000 (Fisher)
	-2, -1	57	(83.8)	57	(82.6)	
Concomitant therapy	Absent	7	(10.3)	11	(15.9)	*P*=0.4491 (Fisher)
	Present	61	(89.7)	58	(84.1)	
Concomitant riluzole	Absent	6	(8.8)	6	(8.7)	*P*=1.0000 (Fisher)
	Present	62	(91.2)	63	(91.3)	
Concomitant drugs other than riluzole	Absent	1	(1.5)	1	(1.4)	*P*=1.0000 (Fisher)
	Present	67	(98.5)	68	(98.6)	

*Factor used in dynamic allocation
Population analyzed: FAS in the double-blind period

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.2.2-1, p. 98-9/550

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Treatment with riluzole was balanced between arms and seen with almost all patients (91.3% in the EDA arm vs. 91.2% in PBO; see Table 10).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was at an acceptable level and slightly higher in the edaravone treatment arm in the double blind period (Appears this way on original

Table **11**) and in the patients continuing on edaravone in the active treatment extension.

Table 11 Treatment Compliance in the Double Blind Portion of Study MCI186-19

Treatment group	Placebo		Edaravone	
No. of patients	68		69	
Treatment compliance	No. of patients	(%)	No. of patients	(%)
100%	61	(89.7)	62	(89.9)
≥90%, <100%	1	(1.5)	6	(8.7)
≥80%, <90%	1	(1.5)	0	(0.0)
≥70%, <80%	0	(0.0)	0	(0.0)
<70%	5	(7.4)	1	(1.4)

Population analyzed: FAS in the double-blind period

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.3.1-1, p.101/550

Efficacy Results – Primary Endpoint

The change (mean ± SD) from "baseline in Cycle 1" to "the end of Cycle 6 (or discontinuation, LOCF)" for the ALSFR-S was −4.4±3.8 in the edaravone group and −6.8±4.9 in the placebo group.

The difference between "at baseline in Cycle 1" and "the end of Cycle 6 or at discontinuation" was analyzed using factors in a dynamic allocation as covariates ("change in ALSFRS-R score from the beginning to the end of the pre-observation period (12 weeks after pre-registration)" (Table 12); "El Escorial revised Airlie House diagnostic criteria"; and "age".) to perform group comparisons. For patients whose data "at the end of Cycle 6" was missing, data was imputed with the last observation carried forward (LOCF). The least square mean (LSMean) ± standard error (SE) for each treatment group was −5.01±0.64 for the edaravone group and −7.50±0.66 for the placebo group. Thus, the LSMean ± SE of the difference between the groups (edaravone group – placebo group, the same applies hereinafter) and the 95% confidence interval of this mean was 2.49±0.76 (0.99 to 3.98), and the difference between the groups was statistically significant (*P*=0.0013).

Table 12 Analysis of Change in ALSFRS-R Score from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (FAS)

Factor	Numerator degrees of freedom	Denominator degrees of freedom	*F*-value	*P*-value
Treatment	1	129	*F*=10.81	*P*=0.0013
Change in ALSFRS-R score during the pre-observation period	1	129	*F*=3.41	*P*=0.0670
El Escorial revised Airlie House diagnostic criteria	1	129	*F*=0.01	*P*=0.9039
Age	1	129	*F*=0.02	*P*=0.8985

Population analyzed: FAS in the double-blind period

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.4.1.1-2, p. 107/550

Application of two-sample t-tests for the difference between baseline and the result of the ALSFRS-R Total Score at the end of each cycle suggests that these results are nominally significant by the end of the 3rd cycle (**Table 13**).

Table 13 Summary statistics for ALSFRS-R score (FAS)

Table 11.4.1.1-1 Summary statistics for ALSFRS-R score (FAS)

Time point	Treatment group	Summary statistics						Summary statistics for change from baseline in Cycle 1							Two-sample *t*-test
		No. of patients	Mean	SD	Minimum	Median	Maximum	No. of patients	Mean	SD	Minimum	Median	Maximum	Paired *t*-test	
Before pre-registration	Placebo	68	43.5	2.2	39	44.0	48	68	1.7	0.8	1	2.0	4	*P*<.0001	*P*=0.9437
	Edaravone	69	43.6	2.2	38	44.0	48	69	1.7	0.9	1	1.0	4	*P*<.0001	
At baseline in Cycle 1	Placebo	68	41.8	2.2	37	42.0	47								
	Edaravone	69	41.9	2.4	36	42.0	47								
At the end of Cycle 1	Placebo	67	40.9	2.9	33	41.0	47	67	-0.9	1.6	-6	0.0	1	*P*<.0001	*P*=0.2658
	Edaravone	69	41.2	2.7	35	42.0	47	69	-0.7	0.9	-3	0.0	1	*P*<.0001	
At the end of Cycle 2	Placebo	66	40.0	3.2	31	40.0	47	66	-1.8	2.1	-8	-1.0	1	*P*<.0001	*P*=0.1767
	Edaravone	67	40.5	3.2	32	41.0	47	67	-1.4	1.7	-8	-1.0	1	*P*<.0001	
At the end of Cycle 3	Placebo	65	39.0	3.5	29	39.0	46	65	-2.9	2.7	-10	-3.0	1	*P*<.0001	*P*=0.0392
	Edaravone	68	39.9	3.8	29	40.5	47	68	-2.0	2.3	-11	-1.0	1	*P*<.0001	
At the end of Cycle 4	Placebo	63	37.8	4.1	28	37.0	46	63	-4.1	3.2	-12	-4.0	2	*P*<.0001	*P*=0.0268
	Edaravone	68	39.0	4.2	26	40.0	47	68	-2.9	2.9	-14	-2.5	1	*P*<.0001	
At the end of Cycle 5	Placebo	63	36.3	5.1	22	37.0	46	63	-5.6	4.5	-18	-4.0	1	*P*<.0001	*P*=0.0041
	Edaravone	68	38.3	4.7	25	39.0	47	68	-3.6	3.2	-15	-3.0	1	*P*<.0001	
At the end of Cycle 6	Placebo	61	34.9	5.7	19	35.0	45	61	-6.9	5.1	-20	-5.0	0	*P*<.0001	*P*=0.0018
	Edaravone	68	37.5	5.3	24	38.5	47	68	-4.4	3.8	-16	-4.0	1	*P*<.0001	
At the end of Cycle 6 (or at discontinuation)*	Placebo	66	35.0	5.6	19	35.0	45	66	-6.8	4.9	-20	-5.0	0	*P*<.0001	*P*=0.0016
	Edaravone	68	37.5	5.3	24	38.5	47	68	-4.4	3.8	-16	-4.0	1	*P*<.0001	

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

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.4.1.1-1, p. 106/550

Primary Analysis – Sensitivity Analyses

Evaluation of the primary outcome by different analyses consistently suggested the primary analysis result is statistically positive (Table 14). An analysis of the primary endpoint by timepoint using

repeated measures analysis replicated the finding in Table 13 of the treatments being statistically different by the end of the third cycle.

Table 14 Results of Sensitivity Analyses on the Primary Analysis

Method	**Adjusted means** edaravone placebo	**Between-group difference in adjusted mean**	
		LSMean ± SE (95% CI)	**P-value**
Repeated measurements analysis of variance for **ALSFRS-R score**	39.12±0.38 37.85±0.39	1.27±0.44 (0.40, 2.14)	P=0.0044
Analysis using the **mean change** in ALSFRS-R score across all cycles as a summary measure	-2.83±0.37 -4.02±0.38	1.19±0.44 (0.31, 2.06)	P=0.0081
Analysis using the slope of time-dependent **mean change** in ALSFRS-R score as a summary measure	-0.88±0.12 -1.35±0.12	0.47±0.14 (0.19, 0.74)	P=0.0010
Analysis taking into account individual differences in the slope of time-dependent **mean change** in ALSFRS-R score **(x/month)**	-0.74±0.08 -1.21±0.11	0.47±0.13 (0.21, 0.73)	P=0.0005

A Kaplan-Meier analysis was performed using the "change in ALSFRS-R score during the pre-observation period" as the stratification factor, for which a decrease in the ALSFRS-R score of ≥6 points as compared with baseline in Cycle 1 was defined as an event and the absence of a decrease of ≥6 points was defined as a censored value, and a stratified log-rank test and stratified generalized Wilcoxon test were performed. The number of events, in the case where an event was defined as "a decrease of ≥6 points," was determined to be 23 in the edaravone group and 33 in the placebo group, and the difference between the groups was significant (P=0.0338 [stratified log-rank test], P=0.0180 [stratified generalized Wilcoxon test]). The number of events when defined as "a decrease of ≥12 points" was 5 in the edaravone group and 13 in the placebo group, and the difference between the groups was significant (P=0.0261 [stratified log-rank test], P=0.0208 [stratified generalized Wilcoxon test]).

Medical Officer's Comments and Analyses: The sensitivity analyses are supportive of the effect demonstrated by the primary analysis.

I performed independent analyses to explore the data supporting the primary endpoint. As a first step, my first analysis was to determine whether the data for the ALSFRS-R Change from Baseline as well as the Total Score were normally distributed or not. Assessment of the dataset ADALS provided by the applicant demonstrated these were not normally distributed through significant results on the Shapiro-Wilk test, so a nonparametric analysis was chosen.
My Evaluation of the median scores for the ALSFRS confirms the significance of the total score as well as the bulbar and limb subscale scores (Table 15).

Table 15 Median Effects by Treatment on ALSFRS-R and its Subscales by Treatment (Study 19 FAS)

Parameter	ARM	Baseline (Median)	Value at Endpoint (Median)	Change from Baseline (Median); Nominal P value
ALSFRS-R (Bulbar function)	Edaravone	11	11	0 (p = 0.0348 Wilcoxon)
	Placebo	11	10	-1
ALSFRS-R (Limb function)	Edaravone	19	17	-2 (p = 0.0006 Wilcoxon)
	Placebo	19	15	-4
ALSFRS-R (Respiratory function)	Edaravone	12	12	0 (p = 0.1587 Wilcoxon)
	Placebo	12	12	0
ALSFRS-R (Total)	Edaravone	42	38.5	-4 (p = 0.003 Wilcoxon)
	Placebo	42	35	-5

Source: Medical Officer analysis of ADALS and ADSL datasets from Study 19

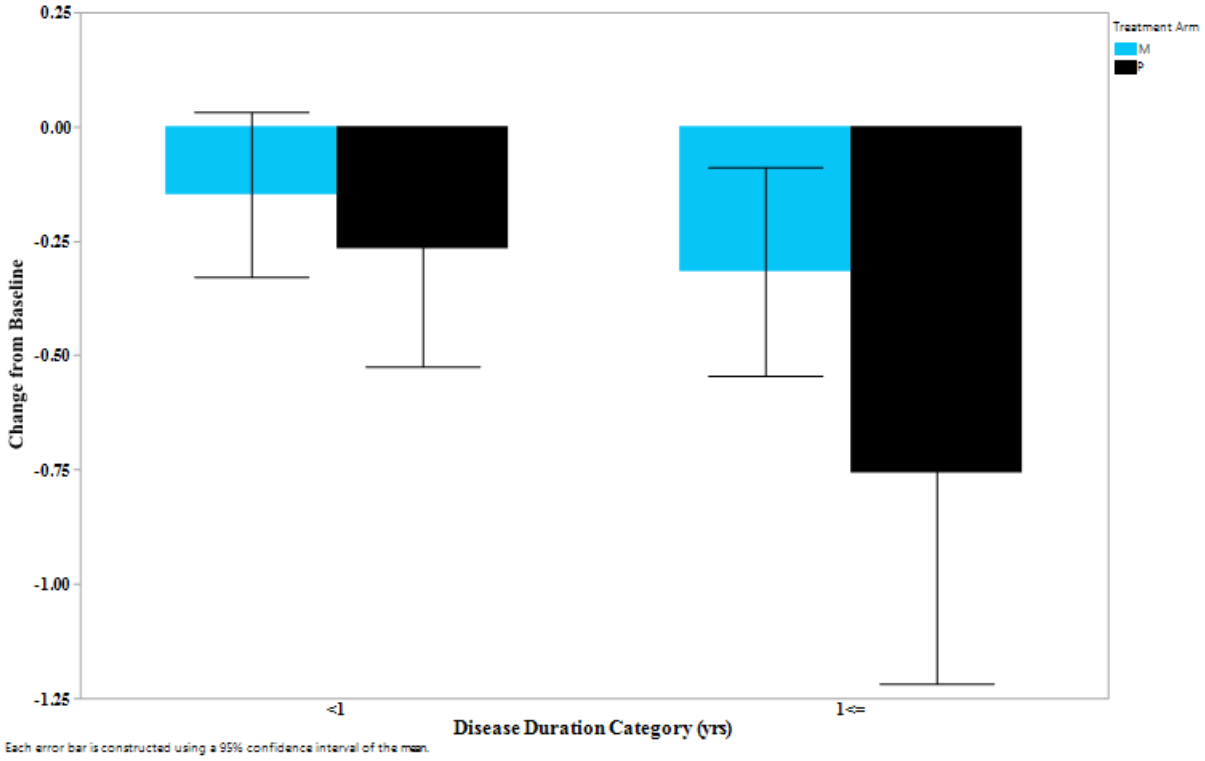
I further investigated this endpoint through graphic means and these exploratory analyses suggest the following:

- **The effect is similar in both genders When accounting for both gender and weight, it appears the drug effect is the same irrespective of weight; This analysis suggested, not unexpectedly, that patients below the mean weight for their gender group, showed the greater disease progression on average**
- **The drug seemed to work the same across age groups, with a decrement in ALSFRS-R total score in both treated and untreated patients over 50 years of age**
- **If the weight was above the mean in older (>50) patients, the difference between drug and placebo seemed less pronounced**

I graphically explored the relationships of disease duration with the ALSFRS-R Respiratory subscale. The magnitude of the drug effect seemed similar for patients of different disease duration (Figure 4 B).

Figure 4 Graphic analysis of the ALSFRS-R Respiratory Component

Disease Duration and Treatment



Efficacy Results – Secondary and other relevant endpoint

Secondary endpoints yielded mixed results with some of the more functional endpoints being nominally positive in favor of edaravone or trending in the direction favoring the active treatment (Table 16) though this must be tempered by the fact that the applicant did not address the issue of multiplicity a priori, by not using techniques to address inflation of alpha when testing the secondary endpoints.

Table 16 Secondary Endpoints of Study 19

Analysis/Endpoint	LSMean ± SE EDA/PBO	Between-group difference in LSMean ± SE (95% CI)	Nominal P-Values
Time to death or certain disease progression, [log-rank test]			*P*=0.1284
Analysis of change in %FVC from baseline in Cycle 1 to the end of Cycle 6 (LOCF)	-15.61±2.41 -20.40±2.48	4.78±2.84 (-0.83, 10.40)	*P*=0.0942
Analysis of change in modified Norris Scale score (total) from baseline in Cycle 1 to the end of Cycle 6 (LOCF)	-15.91±1.97 -20.80±2.06	4.89±2.35 (0.24, 9.54)	*P*=0.0393
Analysis of change in ALSAQ40 score from baseline in Cycle 1 to the end of Cycle 6 (LOCF) (higher score = less favorable)	17.25±3.39 26.04±3.53	-8.79±4.03 (-16.76, -0.82)	*P*=0.0309
Analysis of change in grip strength (Kg; mean of the right and left hands) from baseline in Cycle 1 to the end of Cycle 6 (LOCF)	-4.08±0.54 -4.19±0.56	0.11±0.64 (-1.15, 1.38)	*P=0.8583*
Analysis of change in pinch grip strength (Kg; mean of the right and left hands) from baseline in Cycle 1 to the end of Cycle 6 (LOCF)	-0.78±0.14 -0.88±0.14	0.10±0.16 (-0.23, 0.42)	*P=0.5478*

Time to death or certain disease progression
A log-rank test and generalized Wilcoxon test were performed. In this case, the censoring date was the day when the last observation was performed. For patients who completed the double-blind period, this was the end of Cycle 6 and for patients who discontinued treatment; it was 2 weeks after the last dose. Although there were fewer events in the edaravone group as compared with the placebo group (Table 17), the difference was not nominally significant (P=0.1284 [log-rank test], P=0.1415 [generalized Wilcoxon test].

Table 17 Number of events involving death or certain disease progression (FAS)

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

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.4.1.1-12, p. 119/55

Treatment effects for the Japanese ALS Severity Scale (JALSS) were not formally analyzed by the applicant (Table 18). I plotted the percent of each treatment arm in each of the 5 categories of the JASS at the end of Cycle 6. I used a stacked bar graph to represent patients with a Baseline Category of 1 (blue) or 2 (pink) (Figure 5). There are not significant differences between the two groups, though it appears that the placebo group has a greater proportion of patients showing increased disability, which is represented by higher percentages in Categories 3-5.

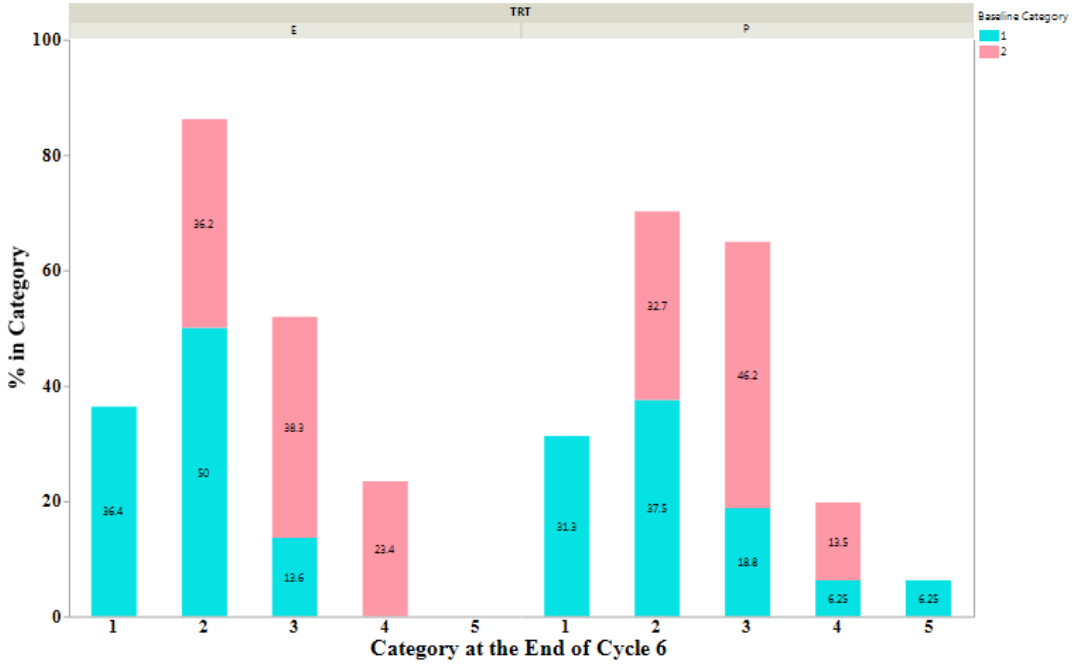
Table 18 Shifts in the Japan ALS severity classification (FAS)

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

Population analyzed: FAS in the double-blind period

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.4.1.1-40, p 152/550

Figure 5 Japanese ALS Severity Scale Categories of Patients at the End of Cycle 6 in the Double Blind Phase of Study 19.

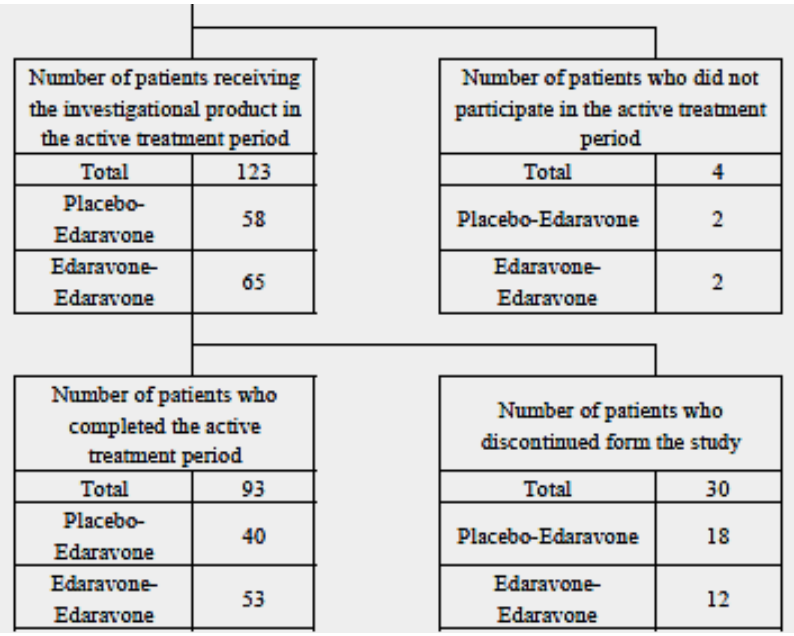


Durability of Response (Discussion of the Active Treatment Portion of Study 19)

The edaravone program did not have long term (e.g., one year or greater) randomized, controlled studies to evaluate the duration of response. Data from Cycles 7 through 12 of Study 19 provides open label data where patients previously on placebo were switched to active treatment. No formal statistical analyses were performed, although comparisons between the placebo-edaravone and edaravone-edaravone cohorts were described.

123 of the 127 patients who completed the Double-Blind portion continued onto the Active-Treatment Portion of Study 19.

Figure 6 Disposition of patients in the active Treatment Phase of Study 19



Source: CSR_Protocol:MCI186-19_ver.2.0, Figure 10.1.2-1

A slightly higher percentage of patients in the Placebo-Edaravone arm (18(31%)) than those continuing on Edaravone (12(18.5%)) discontinued during the Active Treatment Phase of Study 19. Reasons for discontinuation were generally balanced between the two groups (Table 19).

Table 19 Reasons for Discontinuation in the Active Treatment Phase of Study 19

Group	Placebo-Edaravone		Edaravone-Edaravone	
No. of patients	58		65	
Reasons for discontinuation	No. of patients	(%)	No. of patients	(%)
1: The patient requested discontinuation.	7	(12.1)	6	(9.2)
2: The patient was found to be clearly ineligible for the study.	0	(0.0)	0	(0.0)
3: The investigator (or subinvestigator) decided it difficult to continue the patient's participation in the study due to an adverse event, etc.	2	(3.4)	1	(1.5)
4: Tracheotomy was required.	0	(0.0)	0	(0.0)
5: Respiratory support was required all day long.	3	(5.2)	0	(0.0)
6: The investigator (or subinvestigator) decided it inappropriate to continue the patient's participation in the study due to worsening of the primary disease.	0	(0.0)	1	(1.5)
7: The patient underwent spinal surgery for cervical spondylosis, intervertebral disc hernia, etc.	0	(0.0)	0	(0.0)
8: The patient showed %FVC of ≤50% and $PaCO_2$ (blood gas) of ≥45 mmHg.	6	(10.3)	4	(6.2)
9: The patient showed the creatinine clearance of ≤50 mL/min.	0	(0.0)	0	(0.0)
10: Other cases where the investigator (or subinvestigator) decided that the patient's participation in the study should be terminated.	0	(0.0)	0	(0.0)

Population analyzed: FAS in the active treatment period

Source: CSR_Protocol:MCI186-19_ver.2.0,Table 10.1.2-3

Slightly more patients with more favorable ALSFRS-R and JALSSC scores entered into the active treatment phase of Study 19 (Table 20).

Table 20 Demographic and other baseline characteristics at baseline in Cycle 7 (FAS)

Treatment group			Placebo-Edaravone		Edaravone-Edaravone	
No. of patients			58		65	
Variable			No. of patients	(%)	No. of patients	(%)
At baseline in Cycle 7	Japan ALS severity classification	Grade 1	5	(8.6)	8	(12.3)
		Grade 2	22	(37.9)	27	(41.5)
		Grade 3	24	(41.4)	21	(32.3)
		Grade 4	7	(12.1)	9	(13.8)
		Grade 5	0	0	0	0
	ALSFRS-R score	No. of patients	58		65	
		Mean	34.8		37.8	
		SD	5.8		4.9	
		Minimum	19		25	
		Median	35		39	
		Maximum	45		47	

The value listed for each item was obtained at baseline in Cycle 7 (the end of Cycle 6).

Population analyzed: FAS in the active treatment period

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.2.2-2, p.100/550

Treatment compliance was at an acceptable level and slightly higher in the edaravone treatment arm in the patients continuing on edaravone in the active treatment extension (**Table 21**).

Table 21 Treatment Compliance in the Active Treatment Period of Study MCI186-19

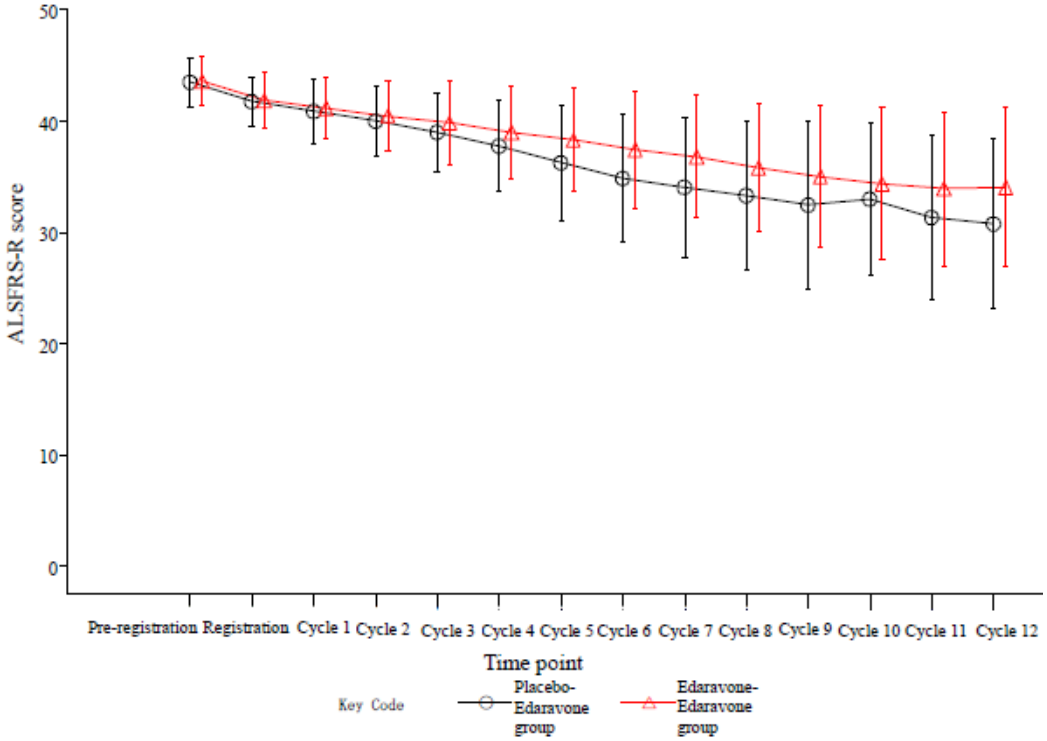
Treatment group	Placebo-Edaravone		Edaravone-Edaravone	
No. of patients	58		65	
Treatment compliance	No. of patients	(%)	No. of patients	(%)
100%	35	(60.3)	48	(73.8)
≥90%, <100%	4	(6.9)	6	(9.2)
≥80%, <90%	5	(8.6)	3	(4.6)
≥70%, <80%	1	(1.7)	1	(1.5)
<70%	13	(22.4)	7	(10.8)

Population analyzed: FAS in the active treatment period

Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.3.2-1, p.103/550

It is difficult to draw any conclusions about the duration of efficacy from the Cycle 7-12 data from Study 19. Also noteworthy is that there is no clear change in the slope of the trajectory of the placebo arm (c.f., Figure 7). This could be due to the relatively short period prior to treatment switch or because the window of opportunity to demonstrate effect has passed for these patients. This is consistent with the applicant's hypothesis that the drug has its greatest effect early in the disease.

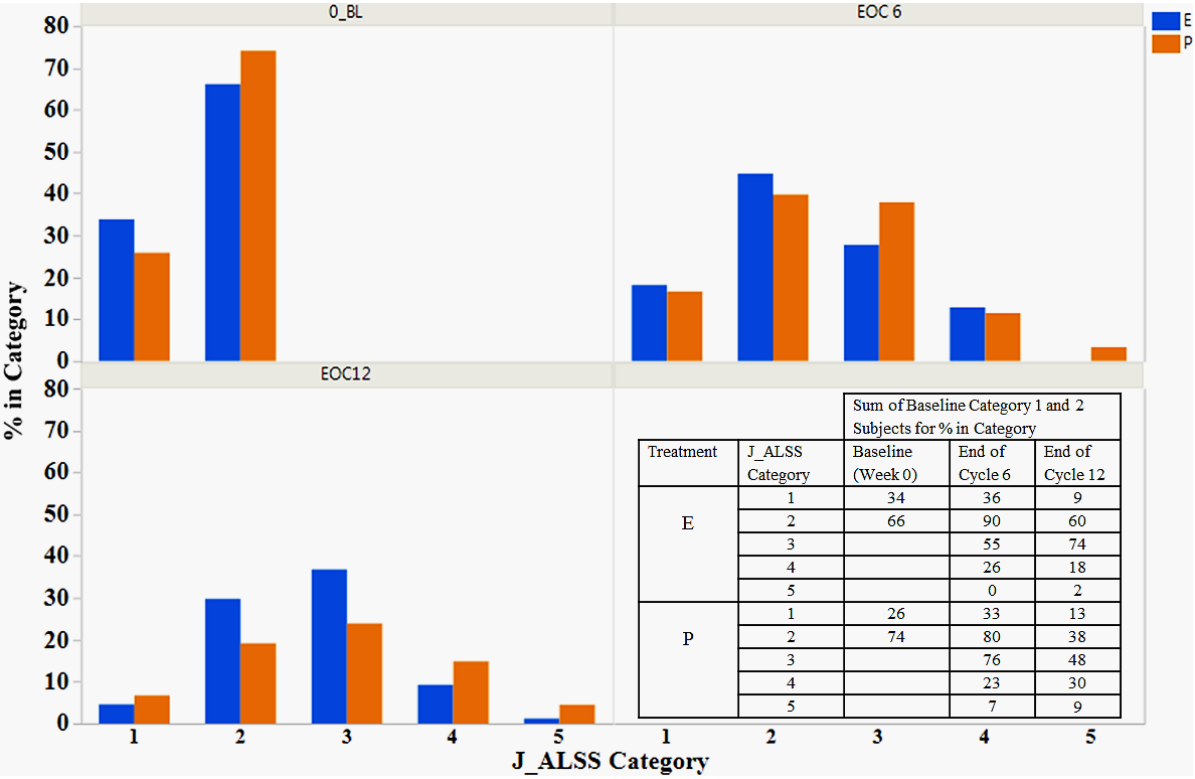
Figure 7 ALSFRS-R results including Active Treatment Portion of Study 19



Source: CSR_Protocol:MCI186-19_ver.2.0, Table 11.3.2-1, p.

I also evaluated the JALSS scale data in the same manner as described for the double blind portion but without regard to the baseline score (see Figure 5). No striking effects were observed however the patients previously treated with placebo have a greater proportion in the more advanced categories (3-5) (Figure 8).

Figure 8 Shifts in the JALSS Scale in Study 19



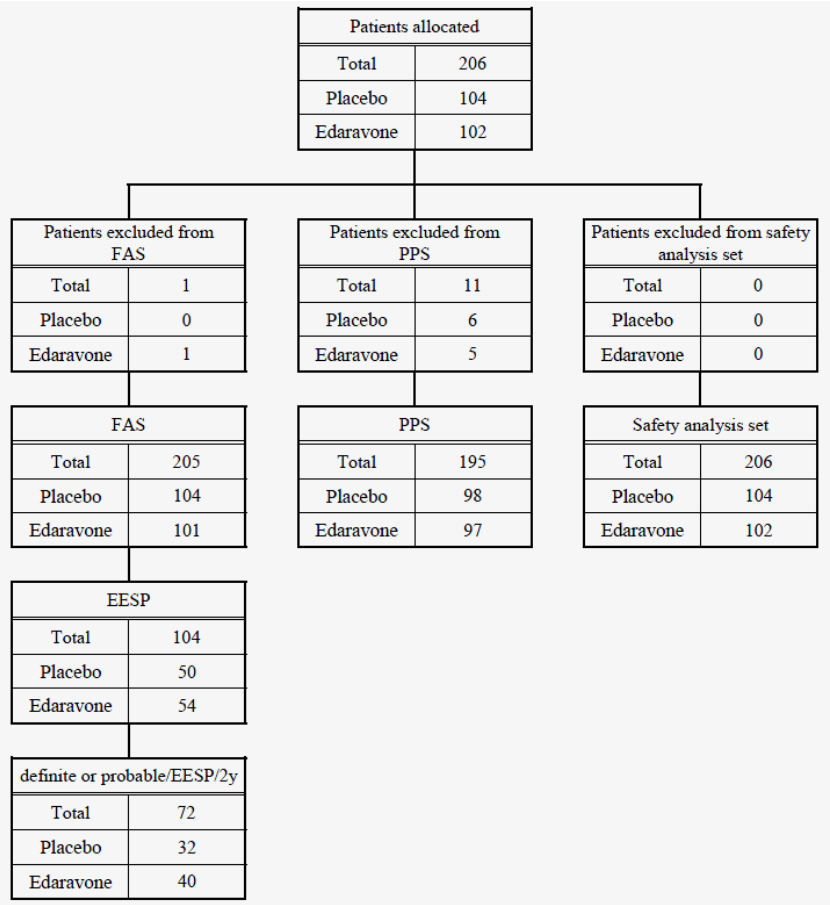
Treatment	J_ALSS Category	Sum of Baseline Category 1 and 2 Subjects for % in Category: Baseline (Week 0)	End of Cycle 6	End of Cycle 12
E	1	34	36	9
	2	66	90	60
	3		55	74
	4		26	18
	5		0	2
P	1	26	33	13
	2	74	80	38
	3		76	48
	4		23	30
	5		7	9

6.2.1. **MCI186-16**

Disposition

Figure 9 demonstrates the disposition of patients in Study 16, including those included in the populations defined post hoc, e.g., EESP and Definite or Probable /EESP/2Y. Allocated patients correspond to randomized patients. Only 1 subject randomized was excluded from the FAS; this was for having a disease other than ALS.

Figure 9 Disposition of Patients in A Priori and Ad Hoc Defined Populations



Source CSR_Protocol:MCI186-16_ver.2.0, Figure 11.1-1, p. 90/772

Table 23 highlights the notable differences between the FAS population from Study 16 and the populations defined in their post-hoc analysis plan, as well as the cases where there was a notable difference between the active and placebo arms in the two post hoc populations.

Table 22 Demographics of the Populations in Study 16

Group		Placebo		Edaravone		Test
No. of patients		104		101		
Factor		n	(%)	n	(%)	
Sex	Male	69	(66.3)	63	(62.4)	$P = 0.5633$ (Fisher)
	Female	35	(33.7)	38	(37.6)	
Age (years)	n	104		101		$P = 0.8973$ (2-sample t-test)
	Mean	57.7		57.9		
	S.D.	10.2		9.8		
	Min.	28		29		
	Median	58.5		58.0		
	Max.	75		73		
	< 20 years	0	(0.0)	0	(0.0)	$P = 0.9971$ (2-sample Wilcoxon test)
	≥ 20 years, < 30 years	1	(1.0)	1	(1.0)	
	≥ 30 years, < 40 years	6	(5.8)	5	(5.0)	
	≥ 40 years, < 50 years	17	(16.3)	10	(9.9)	
	≥ 50 years, < 60 years	31	(29.8)	39	(38.6)	
	≥ 60 years, < 70 years	33	(31.7)	36	(35.6)	
	≥ 70 years	16	(15.4)	10	(9.9)	
	< 65 years	71	(68.3)	73	(72.3)	$P = 0.5451$ (Fisher)
	≥ 65 years	33	(31.7)	28	(27.7)	
Height (cm)	n	104		101		$P = 0.6687$ (2-sample t-test)
	Mean	163.4		162.9		
	S.D.	8.2		8.3		
	Min.	146		145		
	Median	163.0		163.0		
	Max.	182		180		
Body weight (kg)	n	104		101		$P = 0.6175$ (2-sample t-test)
	Mean	59.0		58.3		
	S.D.	12.1		8.8		
	Min.	37		35		
	Median	57.0		57.0		
	Max.	109		77		
Duration of disease (years)	n	104		101		$P = 0.1041$ (2-sample t-test)
	Mean	1.30		1.44		
	S.D.	0.63		0.63		
	Min.	0.3		0.4		
	Median	1.20		1.30		
	Max.	3.0		2.9		
	< 1 year	37	(35.6)	29	(28.7)	$P = 0.0876$ (2-sample Wilcoxon test)
	≥ 1 year, < 2 years	54	(51.9)	49	(48.5)	
	≥ 2 years	13	(12.5)	23	(22.8)	
Initial symptom*	Bulbar symptoms	20	(19.2)	18	(17.8)	$P = 0.8583$ (Fisher)
	Limb symptoms	84	(80.8)	83	(82.2)	
ALS diagnosis	Sporadic	100	(96.2)	100	(99.0)	$P = 0.3691$ (Fisher)
	Familial	4	(3.8)	1	(1.0)	

* Factors for dynamic allocation

Group			Placebo		Edaravone		Test
No. of patients			104		101		
Factor			n	(%)	n	(%)	
El Escorial revised Airlie House diagnostic criteria		Definite ALS	21	(20.2)	29	(28.7)	$P = 0.3070$ (χ^2 Test)
		Probable ALS	54	(51.9)	52	(51.5)	
		Probable ALS Laboratory supported	28	(26.9)	20	(19.8)	
		Possible ALS	1	(1.0)	0	(0.0)	
		Suspected ALS	0	(0.0)	0	(0.0)	
ALS severity classification		Grade I	40	(38.5)	36	(35.6)	$P = 0.7725$ (Fisher)
		Grade II	64	(61.5)	65	(64.4)	
		Grade III					
Rationale for ALS diagnosis	Upper motor neuron dysfunction	No	0	(0.0)	0	(0.0)	–
		Yes	104	(100.0)	101	(100.0)	
	Lower motor neuron dysfunction	No	0	(0.0)	0	(0.0)	–
		Yes	104	(100.0)	101	(100.0)	
	Acute denervation findings in needle electrode exam.	No	4	(3.9)	3	(3.0)	$P = 1.0000$ (Fisher)
		Yes	99	(96.1)	98	(97.0)	
		Not tested	1		0		(excluding patients not tested)
Concomitant use of riluzole*		No	12	(11.5)	11	(10.9)	$P = 1.0000$ (Fisher)
		Yes	92	(88.5)	90	(89.1)	
Complications		No	13	(12.5)	13	(12.9)	$P = 1.0000$ (Fisher)
		Yes	91	(87.5)	88	(87.1)	
ALSFRS-R score during the pre-observation period	Before pre-registration	n	104		101		$P = 0.0650$ (2-sample t-test)
		Mean	43.3		42.5		
		S.D.	2.6		3.4		
		Min.	35		31		
		Median	44.0		43.0		
		Max.	48		48		
	At baseline in Treatment cycle 1	n	104		101		$P = 0.1464$ (2-sample t-test)
		Mean	41.2		40.6		
		S.D.	2.9		3.5		
		Min.	32		29		
		Median	42.0		41.0		
		Max.	47		47		
	Changes from before pre-registration to at baseline in Treatment cycle 1*	–4	11	(10.6)	8	(7.9)	$P = 0.3328$ (2-sample Wilcoxon test)
		–3	21	(20.2)	21	(20.8)	
		–2	39	(37.5)	32	(31.7)	
		–1	33	(31.7)	40	(39.6)	
		–4, –3	32	(30.8)	29	(28.7)	$P = 0.7623$ (Fisher)
		–2, –1	72	(69.2)	72	(71.3)	
Concomitant therapy		No	22	(21.2)	31	(30.7)	$P = 0.1509$ (Fisher)
		Yes	82	(78.8)	70	(69.3)	
Concomitant drug (excluding riluzole)		No	1	(1.0)	1	(1.0)	$P = 1.0000$ (Fisher)
		Yes	103	(99.0)	100	(99.0)	

*: Factors for dynamic allocation

Source CSR_Protocol:MCI186-16_ver.2.0, Figure 11.1-1, p. 90/77

Medical Officer's Comments: **The data suggest the active and placebo arms in the post hoc populations were imbalanced in the variables captured in this table. Not unexpectedly, the post-hoc populations had characteristics generally associated with being at a less severe stage. These imbalances suggest that the -016 study post hoc analysis is not appropriate to consider as a second trial but more so that it supports performing Study MCI-019.**

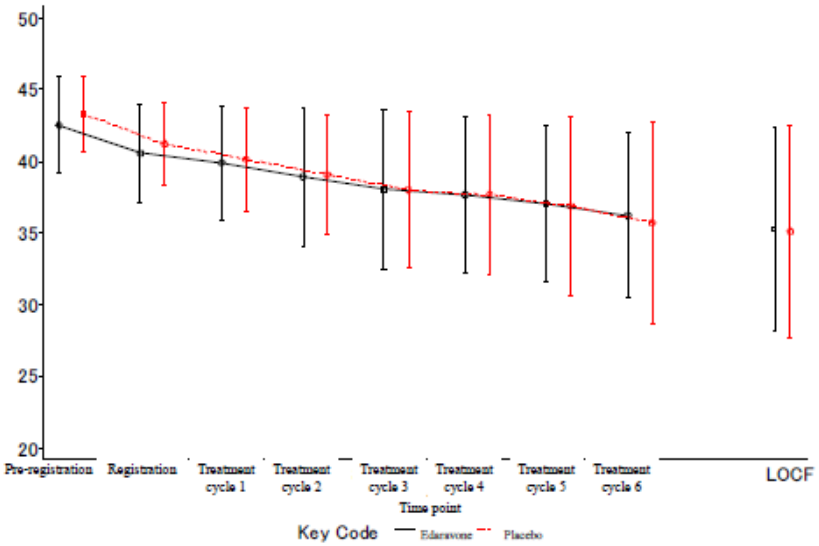
Table 23 Comparison of Baseline Characteristics between Analysis Populations (Study 16)

	FAS		EESP		Definite/or probable/EESP/2Y	
	Placebo	Edaravone	Placebo	Edaravone	Placebo	Edaravone
AGE (yrs)	58.5	58	60	56.5	57	56.5
AGE ≥ 65 (%)	31.7	27.7	36	20.4	25	15
Duration of disease	1.2	1.3	1.05	1.25	0.95	1.2
Diagnostic criteria (% Definite, Probable)	20.2, 51.9	28.7, 51.5	20, 50	35.2, 50	28.1, 71.9	45, 55
ALS Severity (Grade I, II)	38.5, 61.5	35.6, 64.4	48, 52	51.9, 48.1	50, 50	52.5, 47.5
% Concomitant Riluzole	88.5	89.1	82	90.7	78.1	92.5

Primary Endpoint

Figure 10 and Table 24 demonstrate the results of the primary analysis in Study -016. At no point do the results have a statistical separation in the FAS population (Figure 10).

Figure 10 ALSFRS-R Score in Study 16 (FAS)



Source: CSR_Protocol:MCI186-16_ver.2.0, Figure 11.4.4.4-1, p. 98/772

Analysis of the post-hoc populations results in a numerical difference for both EESP and (definite or probable/EESP/2y) groups (Table 24). Paired T-tests of the summary statistics

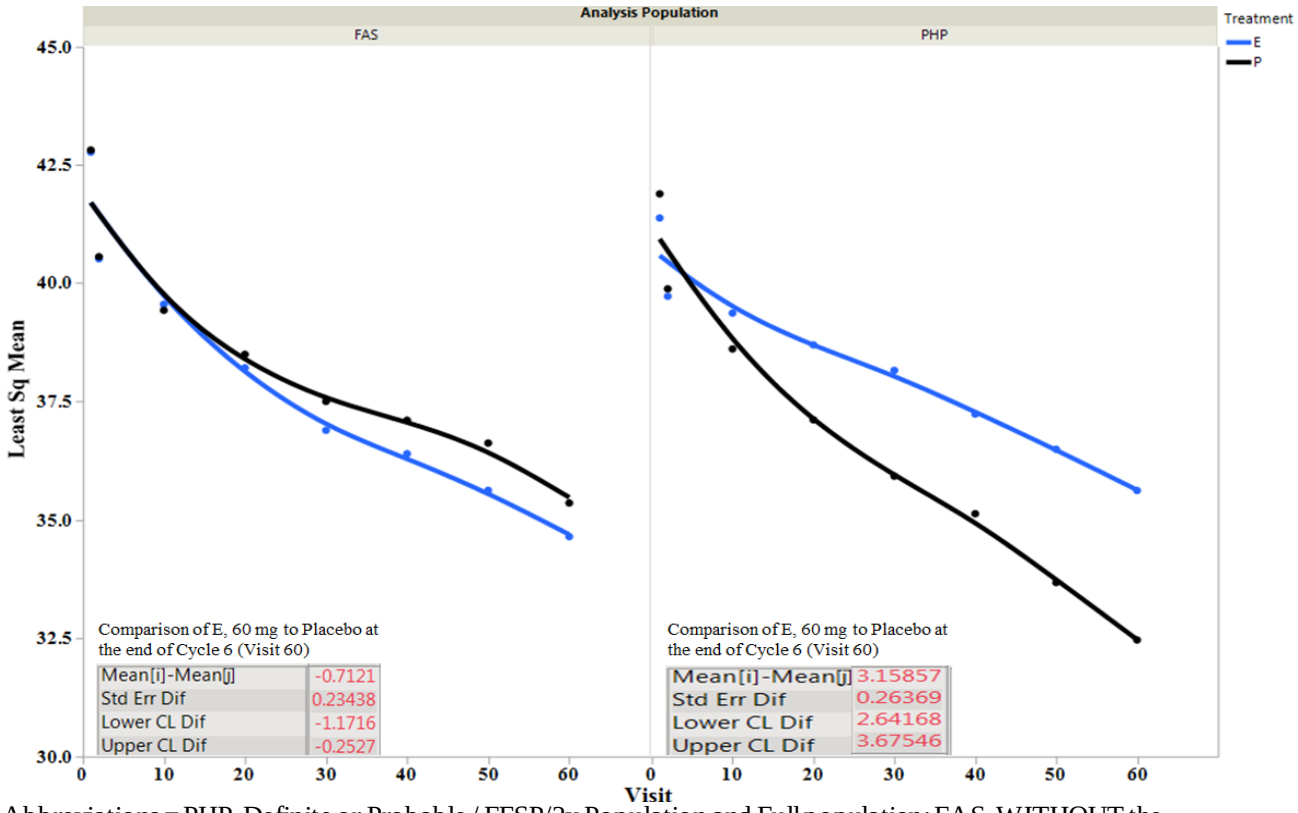
suggest this numeric separation occurs as early as at the end of the first cycle and is maintained though the end of the placebo-controlled period (end of Cycle 6/6 months). Of note, since these evaluations are post-hoc and without correction for multiplicity, all P values are nominal and do not suggest the results are statistically significant.

Table 24 Sensitivity Analyses of the Primary Endpoint in Study 16: Change from Baseline (CFB) and Repeated Measures Analysis (RMA) (FAS and 2 Post-Hoc Populations)

Population	Adjusted LS Mean EDA PBO	Between Group Difference	Nominal P-Value
FAS:CFB	–5.70 ± 0.85 –6.35 ± 0.84	0.65 ± 0.78 (–0.90, 2.19)	0.4108
FAS:RMA	38.08 ± 0.47 37.43 ± 0.46	0.65 ± 0.44 (–0.22, 1.52)	0.1415
EESP:CFB	-4.85 ±1.24 -7.06 ±1.13	2.20 ±1.03 (0.15 , 4.26)	0.0360
EESP:RMA	40.51 ±0.70 38.87 ±0.63	1.64 ±0.58 (0.48 , 2.80)	0.0061
Definite or Probable / EESP/2y:CFB	-4.58 ±1.55 -7.59 ±1.34	3.01 ±1.33 (0.35 , 5.67)	0.0270
Definite or Probable / EESP/2y:RMA	40.75 ±0.88 38.56 ±0.77	2.20 ±0.76 (0.68 , 3.72)	0.0053

Medical Officer's Comments: I performed an analysis to evaluate the effect of edaravone on 'more advanced patients', which was approximated by comparing those in the FAS without the patients in the Definite or Probable / EESP/2y group to this latter post-hoc defined group (Figure 11). My analysis suggests that this population performed slightly worse than placebo numerically, whereas the effect of the post-hoc group without the more advanced population seemed numerically more favorable.

Figure 11 Medical Reviewer's Analysis of the LS Mean ALSFRS of the Definite or Probable / EESP/2y Population and Full population *WITHOUT* the Definite or Probable / EESP/2y the Population.



Abbreviations = PHP, Definite or Probable / EESP/2y Population and Full population; FAS, WITHOUT the Definite or Probable / EESP/2y the Population

Several of the secondary endpoints generally suggested a favorable effect for the post-hoc population, Definite or Probable /EESP/2Y (Table 25). Of note, since these evaluations are post-hoc and without correction for multiplicity, all P values are nominal and do not suggest the results are statistically significant.

Table 25 Applicant Report of Secondary Endpoints by Analysis Population in Study MCI-186-016

ENDPOINT FROM BASELINE IN TREATMENT CYCLE 1 TO THE END OF TREATMENT CYCLE 6 (LOCF)	Mean ± SD (95%CI); Nominal P-Value		
	FAS	**EESP**	**Definite or Probable /EESP/2Y**
Survival analysis on death or certain disease progression [γ]	12(29) vs 14(32); ***0.3814***	2(11) vs 6(13) ***0.6520***	1(8) vs 5(9); ***0.5872***

ENDPOINT FROM BASELINE IN TREATMENT CYCLE 1 TO THE END OF TREATMENT CYCLE 6 (LOCF)	Mean ± SD (95%CI); Nominal P-Value		
	FAS	**EESP**	**Definite or Probable /EESP/2Y**
Change in ALSFRS-R score (bulbar function)	–0.01 ± 0.24 (0.48, 0.47) ; ***0.9761***	0.46 ±0.28 (-0.08, 1.01); ***0.0944***	0.59 ±0.38 (-0.16, 1.35); ***0.1228***
Changes in ALSFRS-R score (limb function)	0.59 ± 0.51 (–0.42, 1.61); ***0.2487***	1.45 ±0.72 (0.01, 2.88); ***0.0480***	2.10 ±0.95 (0.21 , 4.00); ***0.0303***
Changes in ALSFRS-R score (respiratory function)	0.06 ± 0.23 (–0.39, 0.50); ***0.7950***	0.29 ±0.28 (-0.28 , 0.86); ***0.3118***	0.32 ±0.32 (-0.32 , 0.96); ***0.3270***
Changes in %FVC	2.92 ± 2.24 (–1.49, 7.33); ***0.1928***	4.62 ±2.31 (0.02 , 9.21); ***0.0488***	6.30 ±3.10 (0.09 , 12.50); ***0.0467***
Changes in Limb Norris Scale score	1.86 ± 1.50 (–1.11, 4.82); ***0.2178***	5.40 ±2.19 (1.04 , 9.76); ***0.0157***	5.87 ±2.93 (0.02 , 11.73); ***0.0494***
Changes in Norris Bulbar Scale Score	0.17 ± 0.66 (–1.13, 1.48); ***0.7925***	1.46 ±0.91 (-0.35 , 3.27) ***0.1115***	2.07 ±1.18 (-0.30 , 4.44); ***0.0851***
Changes in Modified Norris Scale Total Score	2.03 ± 1.89 (–1.69, 5.75); ***0.2835***	6.86 ±2.74 (1.42 , 12.31); ***0.0141***	7.95 ±3.63 (0.68 , 15.21); ***0.0326***
Changes in ALSAQ40 score	0.48 ± 3.50 (–6.44, 7.39); ***0.8921***	-2.51 ±5.11 (-12.65 , 7.63); ***0.6244***	-3.14 ±6.76 (-16.65 , 10.38); ***0.6442***
Changes in grip strength (mean of left and right)	0.89 ± 0.64 (–0.37, 2.16); ***0.1650***	0.96 ±1.05; (-1.13 , 3.05); ***0.3647***	0.58 ±1.32 (-2.05 , 3.21); ***0.6615***
Changes in pinch grip strength (mean of left and right)	0.20 ± 0.14 (–0.08, 0.48) ***0.1653***	0.38 ±0.23 (-0.08 , 0.84) ***0.1033***	0.20 ±0.31 (-0.42 , 0.82) ***0.5233***

Formal statistical testing was not performed on the Japanese ALS Severity Score however, by my own analysis; it appears that a slightly greater proportion of patients on treatment finished the study in the first 2 categories, which are associated with less severity than Categories with higher numbers (i.e., 3-5).

Medical Officer's Comments: The efficacy results for Study 16 do not stand alone as an adequate and well-controlled trial in support of the application. This opinion is based on the negative primary endpoint and all of the important secondary endpoints. The post-hoc analyses in patients with earlier-stage disease suggest an effect on the ALSFRS, as well as

important endpoints with functional implications including the FVC% and Norris Scale components. Imbalances in the baseline demographics of the post-hoc populations, as well as the fact that it is post-hoc and therefore lacks adequate statistical control, presents issues with arriving at a favorable interpretation of the data; however, on balance, I feel the pharmacodynamic data contribute to the overall evidence for effect of the drug for the proposed indication.

6.3. Summary of Other Phase 2 and 3 Trials

Dosage regimen in all ALS studies in Japan was performed with treatment cycles as follows:
• Cycle 1: 30 mg/30 min (Study MCI186-12 only) or 60 mg/60 min (all Phase III studies) IV administration of edaravone once each day for 14 consecutive days, followed by a 2-week drug-free period
• Cycle 2 and thereafter: 30 mg/30 min (Study MCI186-12 only) or 60 mg/60 min (all Phase III studies) IV administration of edaravone once a day for any 10 days within 2-week period, followed by a 2-week drug-free period.

Study MCI186-12 was a Phase II, open-label, exploratory study for 6 cycles in patients in any stage of ALS. The first group of patients was administered a dose of 30 mg/day (half of the daily dose for AIS), and then the second group of patients was administered 60 mg/day (the same daily dose for AIS).Based on this pilot study, the Sponsor chose 60 mg/day (IV infusion over 60 minutes) as the dose to be tested in all Phase III studies.

Study MCI186-18 was a randomized, placebo-controlled, exploratory study of 25 patients with more advanced ALS (Japan ALS severity grade 3) administered study drug for 6 cycles performed as part of a request by Pharmaceutical and Medical Devices Agency (PMDA). The applicant and PMDA agreed to explore edaravone in the treatment of patients with Japan ALS severity grade 3. However, this study was not powered to detect a statistically significant difference between placebo and edaravone.

There was no difference between treatment groups in the ALSFRS-R score.

Table 26 Change in ALSFRS-R Score from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) for Study MCI186-18 (FAS)

Group	Number of subjects in the LOCF analysis	Adjusted mean change from Baseline	Between-group differences in the adjusted mean	
		LS mean±SE	LS mean±SE (95% CI)	p-value
P group	12	-6.00±1.83	-0.52±2.46 (-5.62, 4.58)	p=0.8347
E group	13	-6.52±1.78		

Note: LOCF was applied to subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.
Source: MCI186-18 CSR.

Source: Clinical Overview, Table 2.5.4-4, p. 30/55

Study MCI186-17 was a multicenter, parallel-group study that was double-blind, placebo-controlled extension of Study 16 for Cycles 7 to 12 (6 cycles) and with all subjects on Active treatment with edaravone for Cycles 13 to 15 (3 cycles). Treatment assignments for this study are depicted in Table 27 (3rd and 4th Columns). A detailed description of this study is not included in this review, since it is not being considered in the body of evidence supporting efficacy.

Table 27 Treatment Assignments for Studies 16 and 17

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

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy across Trials

7.1.1. Primary Endpoints

The post hoc results from Study 16 were used to define the Study 19 full analysis population that was prospectively tested for the primary endpoint; this analysis is found to be statistically significant. Clinical benefit was demonstrated by the fact that patients on drug experienced 2.49 points less decline on the 48-point Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) scale over a 6-month period. This scale measures different functional domains of daily living, as well as patient perception of respiratory insufficiency. Survival was not significantly affected in the studies of this program.

Study 19 is the principle source of evidence for this submission and so integration or integrated analysis of trials for evaluation of efficacy is not useful. However, a key issue of the submission is for what population the drug should be indicated and I believe that issue merits consideration of results from several of the trials as well as of the natural history of ALS. The results from Studies 16 (c.f., Figure 11) and 18 (Section 6.3) suggest the drug may not be effective in patients after some early stage of the disease. While this may be considered for a limitation of use, I believe that the variability in this disease would preclude giving accurate information as to where the effect diminishes. Further, Studies 16 and 18 were not designed to fully evaluate this issue.

7.1.2. Ethnic Considerations / Subpopulations

This section is particularly important for this application since the study population considered for the body of substantial evidence was entirely comprised of patients of Japanese origin. The

applicant has provided information in the following domains to support their case that the Japanese and Caucasian patients are similar and that a similar effect can be expected between the two ethnic groups:

1. Natural History Comparison
   a. Regarding ALS diagnosis in the US based on El Escorial criteria, there is no racial difference reported among White, Black, and Asian populations. The diagnostic cross-section is closely comparable among races, with approximately 40% to 54% of patients diagnosed as Definite ALS, 21% to 23% of patients diagnosed as Probable ALS and 7% to 14% of patients diagnosed as Probable laboratory-supported ALS
   b. The prevalence of ALS thought that is classified as Sporadic versus Familial is the same in the two regions (Table 28).
   c. The percentage with onset originating with bulbar signs is almost the same between the two regions (Table 28).

Table 28 Comparisons of Demographics of ALS in the United States and Japan

	United States	Japan	Reference number
Sporadic ALS (%)	94% to 96%	93%	7,47,48,49
Bulbar onset (%)	32% to 33%	25% to 30%	48,50,51,52
Time from onset to diagnosis (M)[a]	11 to 12 M	11M	46,48,51,52 53
PEG use (%)	9% to 27%	29% to 33%	47,54,55,56,57
TIV use (%)	4%	29% to 34%	56,57,58
Riluzole use (%)	49%	71%	59

Abbreviations: ALS = amyotrophic lateral sclerosis; PEG = percutaneous endoscopic gastrostomy; TIV = tracheostomy with invasive ventilation.

[a] Median time in United States.

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 2.7.3-27, p. 66/86

   d. The progression of ALS in the two regions was studied by comparing data from edaravone studies with that published in 7 ALS Phase II or Phase III studies conducted mainly in the US from 6 drugs as reference, where placebo was administered in double-blind fashion (each study with at least 20 placebo patients to compare slope of ALSFRS-R).

      Demographic comparison is shown in Table 29. All edaravone studies enrolled Japanese patients only while all other reference studies enrolled mainly Caucasian/White (>90% for all studies). Body weights or BMIs were, on average, smaller in edaravone studies than those in the reference studies. Riluzole use was higher in edaravone studies. Disease durations in edaravone studies were shorter especially for Studies 19 and 16 Definite or Probable/EESP/2y population as inclusion criteria required within 2 years from onset of ALS symptom.

Table 29 Comparison of Slope of Time Dependent Change in ALSFRS-R Score between Reference Studies Including US Patients (Upper) and MCI-186 (Edaravone) Studies (Lower)

Study Drug		Celecoxib[63]	Minocycline[64]	TCH346[65]	Ceftriaxone[62]	NP001[66]	Dexprami-pexole[67]	PRO-ACT Database[68]
Phase		-	PIII	PII/III	PI II/III	PII	PII	PII/III
Run-in period		NA	4M	4M	NA	NA	NA	-
Double Blind period		12M	9M	6M	12M	6M	3M	Average12M
Slope Run-in period		-	-0.81± 0.05	-0.771	-	-	-	-
Placebo	N	99	206	108	173	42	27	4838
	Baseline ALSFRS-R[a]	43.24 ± 5.17	37.9± 5.17	-	36.9 ± 5.4	38.2 ± 5.6	37.3 ± 5.14	38.37 ± 5.22
	Slope (change per month)[c]	**-1.078 ± 0.907**	**-1.04 ± 0.07**	**-0.942**	**-1.22 ± 0.06**	**-0.89**	**-1.28**	**-1.02 ± 2.3**
Active	N	201	206	105	340	45	26	-
	Baseline ALSFRS-R[a]	42.88 ± 5.54	37.8 ± 5.17	-	36.5 ± 6.0	37.6 ± 5.0	38.5 ± 5.97	-
	Slope (change per month)[c]	**-1.077 ± 0.0645**	**-1.30 ± 0.07**	**-1.067**	**-1.13 ± 0.04**	**-0.77**	**-0.88**	-
Statistical Model		Mixed model analysis of variance	Linear mixed-effects model	Linear mixed effect model (without 0 imputation at the date of death)	Random slopes regression model	General linear mixed effects model with random effects	Linear mixed effect model	Mixed effect model

Study Drug		Edaravone	Edaravone	Edaravone	Edaravone	Edaravone
Study Number population		**MCI186-19 FAS**	**MCI186-16 dp/EESP/2y**	**MCI186-17 dp/EESP/2y**	**MCI186-16 FAS**	**MCI186-17 FAS**
Run-in period		3M	3M	NA	3M	NA
Double Blind period		6M	6M	6M	6M	6M
Slope Run-in period		-	-	-	-	-
Placebo	N	68	32	16	104	44
	Baseline ALSFRS-R[a]	41.8 ± 2.2	42.2 ± 2.2	38.2 ± 5.1	41.2 ± 2.9	36.5 ± 5.5
	Slope (change per cycle[b]) [c]	**-1.21 ± 0.11**	**-1.21 ± 0.21**	**-0.98 ± 0.22**	**-1.03 ± 0.10**	**-1.04 ± 0.16**
Active	N	69	40	22	101	45
	Baseline ALSFRS-R[a]	41.9 ± 2.4	42.5 ± 2.5	38.4 ± 5.2	40.6 ± 3.5	36.5 ± 5.6
	Slope (change per cycle[b])[c]	**-0.74 ± 0.08**	**-0.69 ± 0.09**	**-0.67 ± 0.13**	**-0.95 ± 0.11**	**-0.72 ± 0.10**
Statistical Model		Random coefficient model				

For MCI186-19 and -16 FAS analyses, the slope analyses were pre-specified in SAP and documented in CSRs.
For MCI186-16 and -17 definite or probable/EESP/2y, and MCI186-17 FAS analyses, the slope analyses were performed as post-hoc for this purpose.
If there were multiple active treatment groups, the highest dose group was used.
[a] Mean = SD.
[b] Cycle = 28 days.
[c] Least Square Mean ± SE.
Source: ISE Table 7.1.1, 7.2.1, and 7.4.1.

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 2.7.3-28, p. 68/86

Slopes of ALSFRS-R score (change per month) on placebo in all reference studies consistently ranged between -0.89 and -1.28/month (between -0.89 and 1.28/month. This is similar with data from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database that included longitudinal data Slopes of ALSFRS-R score (change per month) on placebo in all reference studies ranged from 8,635 people with ALS who enrolled in 17 different clinical studies, which

indicated ALSFRS-R declined by -1.02 ± 2.3 points per month [REF]. The slopes of ALSFRS-R score on placebo in edaravone studies (both FAS and Definite or Probable/EESP/2y) also ranged between -0.98 and -1.21/Cycle (equal to a month) suggesting that the slopes are similar between edaravone studies and reference studies. On the other hand, slopes on active edaravone in the enriched Definite or Probable/EESP/2y population (Study MCI186-19 FAS and Study MCI186-16/-17) range between -0.67 and -0.74, showing less steep declines than the slope of ALSFRS-R in the reference placebo groups.

In addition, the applicant also compared change from Baseline using MMRM analyses because the most recent dexpramipexole Phase III study 61 focused on the change from Baseline in ALSFRS-R score using MMRM analysis rather than change in the slopes of ALSFRS-R score (Table 30). Although the published literature of dexpramipexole study shows 12-month data only, the applicant estimated 6-month data using MMRM analysis from a figure in the literature indicating a change of approximately -7 points from Baseline at 6 months in both placebo and active groups (Figure 12). There were similarities in slopes of the ALSFRS-R score on placebo, as well as changes from baseline on placebo calculated by MMRM analysis, between edaravone studies in Japanese ALS patients and the reference ALS studies including US patients. The range of slopes of ALSFRS-R on active edaravone showed less decline with time (Figure 12).

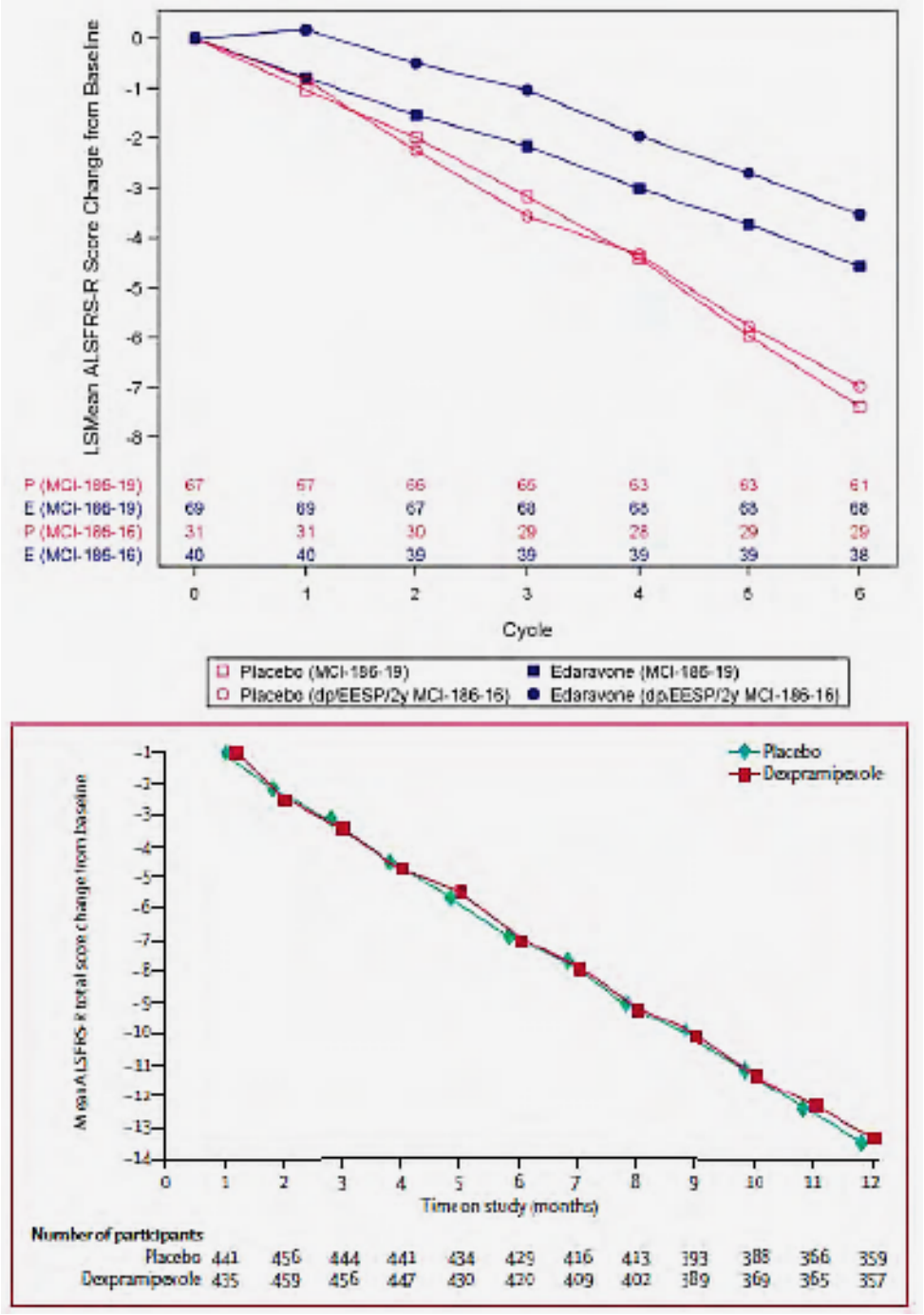
Table 30 Comparison of Change from Baseline in ALSFRS-R Score between Dexpramipexole Phase III Study and MCI-186 (Edaravone) Studies

Study Drug		MCI-186 (edaravone)			Dexpramipexole[61]
Study Number/ Population or Study Phase		MCI186-19 FAS	MCI186-16 dp/EESP/2y	MCI186-17 dp/EESP/2y	PIII
Double Blind period		6M	6M	6M	12M
Placebo	N	61	29	15	468
	Baseline ALSFRS-R[a]	41.8 ± 2.2	42.2 ± 2.3	38.2 ± 5.1	37.9 ± 5.7
	Change from Baseline[b]	-7.37 ± 0.57	-6.97 ± 1.00	-5.85 ± 1.16	-13.42 (12M data)
Active	N	68	38	21	474
	Baseline ALSFRS-R[a]	41.9 ± 2.4	42.5 ± 2.5	38.4 ± 5.2	38.4 ± 5.2
	Change from Baseline[b]	-4.56 ± 0.55	-3.54 ± 0.90	-3.68 ± 0.97	-13.34 (12M data)

[a] Mean ± SD.
[b] Least Square Mean ± SE from MMRM Analyses as post-hoc.
Source: ISE Table 3.1.3, 3.2.3, and 3.5.1.

Source: Module 2.7.3, Summary of Clinical Efficacy, Table 2.7.3-29, p. 69/86

Figure 12 Comparison of Changes from Baseline in ALSFRS-R Scores Calculated by MMRM Analyses



Top: Study MCI186-19 FAS and Study MCI186-16 definite or probable/EESP/2y populations (Source: ISE Figure 1.6.1).
Bottom: Dexpramipexole Phase 3 study (cited from Figure 2 Cudkowicz 2013).
Source: Module 2.7.3, Summary of Clinical Efficacy, Figure 2.7.3-16 2.7.3-29, p. 70/86

2. Comparison of Biomarkers associated with ALS

There are no biomarkers reasonably able to predict the course or severity of disease or treatment effects in ALS. However there are some that show some associations with the disease or that are believed to be involved in countering oxidative pathophysiology. The applicant has provided data on the similarities in some of these in the Japanese and Caucasian populations (Table 31).

Table 31 Relative Changes in Different Ethnic Populations in Biomarkers Associated with ALS

Biomarker	Country (race, if available)	ALS cases	Control	Sampling	Result	Reference
Oxidized DNAs						
8-OHdG	Japan	FALS (n=1) SALS(n=6)	HC (n=14)	CSF	↑8-OHdG in SALS	Ihara Y et al., 2005[11]
8-OHdG	Japan	SALS (n=17)	HC (n=17)	CSF	↑8-OHdG in SALS	Murata T et al., 2008[12]
8-OHdG	US	ALS (n=65)	HC (n=63)	Urine Blood CSF	↑8-OHdG in ALS	Bogdanov M et al., 2000[13]
8-OHdG	US	FALS (n=8) SALS (n=16)	HC (n=63)	Brain Spinal cord	↑ 8-OHdG DNA in SALS motor cortex ↑ 8-OHdG immunoreactivity in both SALS and FALS spinal code	Ferrante RJ et al. , 1997[9]
8-oxo-dG	US	SALS (n=50)	HC (n=46)	Urine	↑8-oxo-dG (creatinine adjusted) in SALS	Mitsumoto H et al, 2008[14]
8-OHdG	France	SALS (n=9)	HC (n=10)	Blood	↑8-OHdG in SALS	Blasco H et al., 2016[15]
Oxidized lipids						
HNE	US	FALS (n=14) SALS (n=108)	HC (n=22)	CSF Blood	↑ Serum HNE in SALS at all stage of disease	Simpson EP et al., 2004[16]
IsoP	US	SALS (n=50)	HC (n=46)	Urine	↑IsoP (creatinine adjusted) in SALS	Mitsumoto H et al, 2008[14]
MDA	France	SALS (n=9)	HC (n=10)	Blood	↑ MDA in SALS	Blasco H et al., 2016[15]
MDA	France	ALS (n=31)	HC (n=30)	Blood	↑ MDA in ALS	Baillet A et al., 2010[17]
Oxidized proteins						
3NT	Japan	SALS (n=19)	HC (n=19)	CSF	↑3-NT in SALS	Tohgi H et al., 1999[18]
3NT	US	ALS (n=14)	HC (n=10)	Spinal cord	↑3-NT concentration in lumber cord of both SALS and FALS. ↑3-NT immunoreactivity in motor neuron of both SALS and FALS	Beal MF et al., 1997[19]
3NT	Sweden	ALS (n=14)	HC (n=19)	CSF	No difference in 3-NT between ALS and HC	Ryberg H et al., 2004[20]
AOPP	Italy	ALS (n=73)	HC (n=68)	Blood	↑AOPP in ALS	LoGerfo A et al., 2014[10]
AOPP	Italy	SALS (n=74)	HC (n=65)	Blood	↑AOPP in SALS	Pasquinelli A et al., 2016[21]
AOPP	Italy	ALS (n=49)	HC (n=8)	CSF Blood	↑AOPP in ALS	Siciliano G et al., 2007[22]
Uric acid						
Uric Acid	Japan	ALS (n=26)	HC (n=55)	Blood	↓Uric Acid in ALS	Nagase M et al., 2015[23]
Uric Acid	Japan	ALS (n=92)	HC (n=92)	Blood	↓Uric Acid in ALS	Ikeda K et al., 2012[24]
Uric Acid	Korea	SALS (n=136)	HC (n=136)	Blood	↓ Uric Acid in ALS	Oh S et al., 2015[25]
Uric Acid	China	SALS (n=512)	HC (n=501)	Blood	↓ Uric Acid in ALS	Zheng Z et al., 2014[26]
Uric Acid	Israel	ALS (n=86)	HC (n=86)	Blood	↓ Uric Acid in ALS	Keizman D et al., 2009[27]
Uric Acid	Italy	ALS (n=132)	HC (n=337)	Blood	↓ Uric Acid in ALS	Zoccolella S et al., 2011[28]

Source: Generalizability between Japan and US: Additional information 0035 (36) Submitted 12/14/2016

3. Clinical diagnostic and assessment comparison – To assess relative similarities and differences that might exist between US and Japanese care of the patient with ALS, the applicant reviewed the following documents:
    a. For Japan, ALS treatment Guidelines of 200233 and ALS Clinical Practice Guidelines of 2013, of the Japanese Society of Neurology
    b. For the US, the Practice parameter: The care of the patient with amyotrophic lateral sclerosis, of the American Academy of Neurology (1999) and its updates (2009)

(b) (4)

(b) (4) has reviewed and concurs with the applicant's assessment of North American and Japanese guidelines and practices that is described as follows:

- Consensus in diagnostic criteria for ALS and the use of physical examination, supported by technology, are essentially identical. Specifically, both the US and Japan utilize the El Escorial diagnostic criteria of the World Congress of Neurology (2000).
- There is a similar recognition of symptoms and their progression in both regions with similar acknowledgement of complications of ALS including cognitive and behavioral impairment, sialorrhea, impaired communication, and swallowing. Similar recognition of the importance of coordinated interdisciplinary care is emphasized.
- The US guidance tends to recognize increased survival when interdisciplinary care is available in specialty centers. The Japanese guidance emphasizes the enhancement of quality of life that is associated with the availability of interdisciplinary care.
- Riluzole, as an oral medical therapy intended to increase survival time in ALS, is available as first line therapy and recommended for prescription in both regions. No other drugs are approved for slowing the progression of ALS. There may be modest differences in some of the medications that are prescribed for secondary complications and symptomatic relief (dependent on the availability of different drugs in the different regions). In 2010-2012, riluzole was reported to be utilized by approximately 70% of ALS patients in Japan and 50% of ALS patients in the US.59 In the context of multiple generic versions of riluzole available in the US since 2013, it is speculated that rates of use are increasing in the US.
- Similar awareness of the important requirements for nutritional support is noted in both regions, with strongly consistent advice regarding the most appropriate time for different interventions, including percutaneous endoscopic gastrostomy (PEG) placement.
- There may appear to be less flexibility in the Japanese written guidelines about the terminal choice of discontinuation of invasive ventilator support, although non-invasive respiratory and ventilatory support, tracheostomy based invasive respiratory support, and various methods of manual and mechanical therapeutic interventions are similarly used. In acknowledging that there may be a difference that is related to the practice of terminal withdrawal of tracheostomy-assisted ventilation in the final stage of the disease, it is reasonable to conclude that this variation in culture of care would not affect the

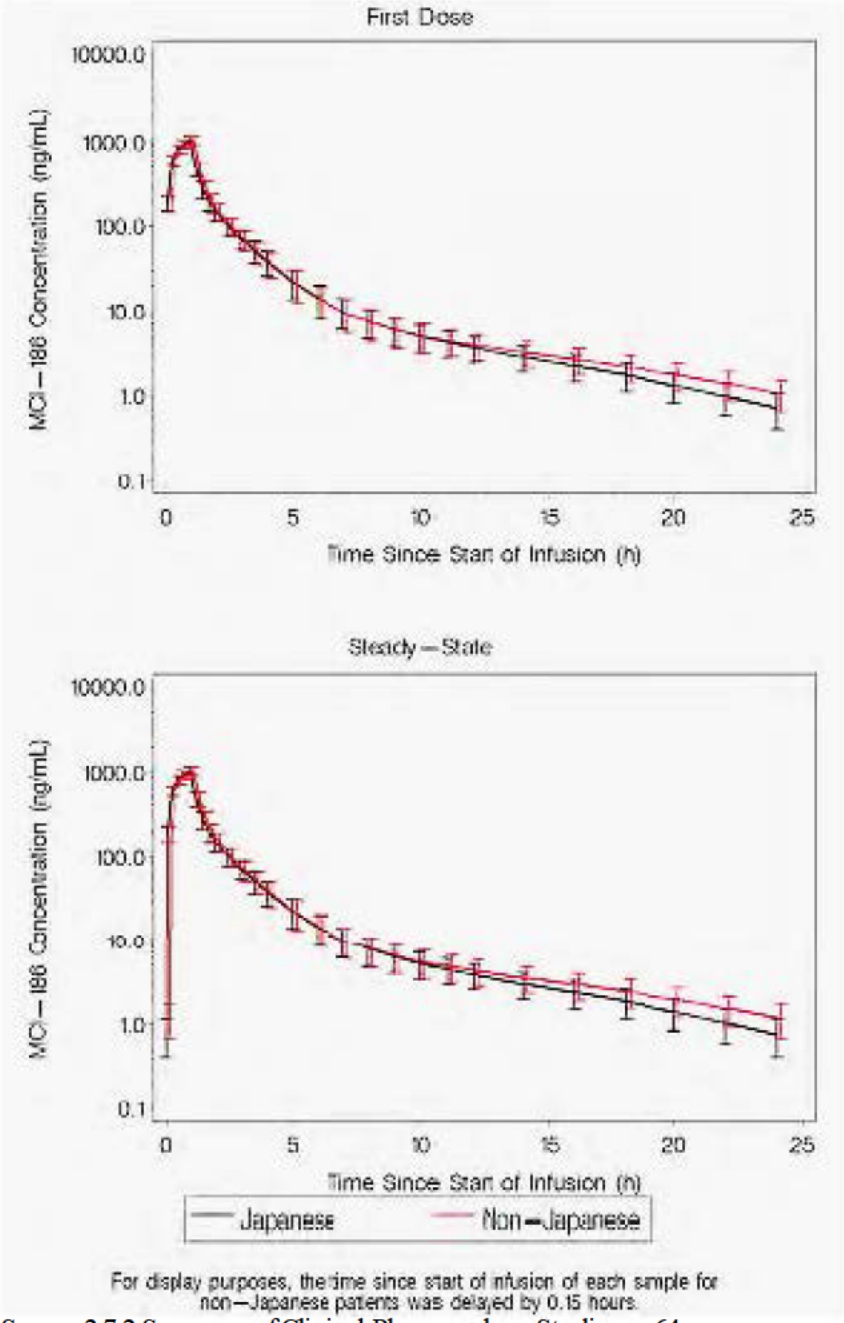
interpretation of data from edaravone studies in ALS where relatively early stage of ALS patients were evaluated for efficacy in the development program for edaravone, where clinical focus is on early disease intervention. Miller et al reported an ALS research outcome in 5600 patients from 1996 to 2005, showing the use of PEG in the US was variable among ALS clinics, ranging from 0% to 52%. Only 9 % of patients underwent PEG although PEG was recommended in 22% of patients. The percentage of PEG use appeared to be increasing with education. Regarding ventilatory support in ALS, Japanese treatment practices39 tend to favor the introduction of tracheostomy with invasive ventilation (TIV) in the later stage of ALS (switching from non-invasive ventilation). The Japanese written treatment guidelines may also be interpreted providing lessened flexibility in terminal discontinuation of invasive ventilatory support. The TIV use is prescribed in Japan in 29% to 34%56, 57 of patients, but is used less commonly in the US (4%).58 This clear difference in tracheotomy and potential difference in PEG use in the late stage ALS is less relevant to relatively early stage of ALS patients who were evaluated for efficacy in the development program for edaravone.

4. Pharmacokinetic comparison – Covariate effects by race, gender (in Caucasians, as Japanese women were not enrolled in Japanese PK studies), weight, and age were investigated to explain variability in the PK model parameters. Gender, age, or weight did not affect any PK parameters. The effect of race was the only one statistically detected, and that effect only for peripheral volume of distribution 2 (V2), indicating a 26% difference in the estimate of V2 between Caucasian and Japanese. Race was not statistically detected as a covariate for any other PK parameter. No effects were observed on any PK parameters by gender, age, or weight. The small difference of V2 by race was associated with a minimal difference of terminal concentration of edaravone (around 1 ng/mL) after each infusion that is far below the 1000 ng/mL at Cmax, and will not result in accumulation or a change of drug concentration. The maximum plasma concentration after administration (Cmax) or area under the plasma concentration-time curve (AUC) of edaravone does not appear to be related to weight (nor age and gender). The metabolic profile is similar between Japanese and Caucasians as demonstrated that the sulfate and then glucuronide are the main metabolites in plasma while the glucuronide and then sulfate are the main metabolites in urine. The pattern of metabolites found in plasma and urine was similar between Japanese patients and Caucasian patients (Module 2.7.2.3.2.1).

   Ethnic differences were evaluated with Population PK simulations using virtual ALS populations (1000 patients for each population) assuming a distribution of gender (62% male in Japanese and 59% in non-Japanese [US/EU]), and assuming normal distributions of weight (average 57.9 kg for Japanese and 77.5 kg for non-Japanese [US/EU]) and age (average 59 years in Japanese and 56 years in non-Japanese [US/EU]) based on data from edaravone studies for Japanese and literature for ALS studies for non-Japanese (US/EU patients). The PK simulation demonstrated no difference in Cmax or AUC between Japanese and non-Japanese (US/EU) after IV infusion of edaravone. The half-lives of each elimination phases (α, β, and γ) after dosing at 60 mg/60 min/subject were calculated using the mean of the simulated plasma concentration of edaravone by time in virtual ALS populations (1000 patients for Japanese and non-Japanese, respectively). The calculated half-lives of each elimination phases (α, β, and γ) in Japanese were 0.15, 0.86,

and 4.41 hours, and those in non-Japanese (US/EU) were 0.15, 0.88, and 6.34 hours, respectively

Figure 13 Simulated Concentration Versus Time Curves For 60 Mg Infusion Of Edaravone Over One Hour



Source 2.7.2 Summary of Clinical Pharmacology Studies, p. 64

Table 32 Simulation results from Population PK Analyses for 60 mg/60 minute infusion QD x 14D (1000 pts/subpopulation)

Simulated Exposure Measure		Japanese		Non-Japanese (US/EU)	
		Day 1	Day 14	Day 1	Day 14
C_{max} (ng/mL)	Mean (SD)	1048.1 (114.2)	1049.3 (114.8)	1046.6 (117.0)	1048.6 (117.6)
	Median	1040	1040	1040	1040
	Min, Max	760, 1430	754, 1430	603, 1510	602, 1520
$AUC_{(0\text{-}24h)}$ (ng*hr/mL)	Mean (SD)	1367.0 (191.2)	1373.5 (193.2)	1362.3 (194.6)	1374.3 (198.6)
	Median	1360	1360	1340	1360
	Min, Max	904, 2050	905, 2070	697, 2160	699, 2190

Source 2.7.2 Summary of Clinical Pharmacology Studies, Table 2.7.2.3.3-1

5. Clinical Comparison – After the Japanese approval in 2001, Study MCI186-13, post-marketing clinical trial in Japanese patients with acute-stage cerebral thrombosis was conducted to compare 30 mg/30 min b.i.d. of edaravone (n=194) and 80 mg b.i.d. of ozagrel sodium (an antiplatelet therapy) (n=198). In Europe, one study in AIS patients was conducted (MCI186-E04). The tested doses were Cohort 1 (n=12); 0.2 mg/kg/hr for 72 hours with initial 0.08 mg/kg of bolus infusion (total dose was approximately 14 mg/kg) and Cohort 2 (n=13); 0.4 mg/kg/hr for 72 hours with initial 0.16 mg/kg of bolus infusion (total dose was approximately 29 mg/kg), and matching placebo cohort (n=11). While there were issues in PK assessment (internal standard determination and outside of sample collection time window with limited PK samples), median C_{max} appeared to reach to approximately 400 ng/mL in Cohort 1 and approximately 1800 ng/mL in Cohort 2. Edaravone concentrations were then set at steady state through 72 hours. There were no notable differences in AEs including laboratory abnormalities among treatment groups and no dose-dependent AEs were observed.

Table 33 Adverse Events from Study MCI-04,a Study in Caucasians

	MCI186-E04					
			Edaravone			
	Placebo (N = 11)		Cohort 1 0.08 mg/kg bolus + 0.2 mg/kg/h infusion (N = 12)		Cohort 2 0.16 mg/kg bolus + 0.4 mg/kg/h infusion (N = 13)	
	n (%)	No. of Events	n (%)	No. of Events	n (%)	No. of Events
AEs	10 (90.9%)	39	12 (100.0%)	34	10 (76.9%)	36
SAEs	1 (9.1%)	1	0	0	2 (15.4%)	3
AEs leading to discontinuation	0	0	1 (8.3%)	1	1 (7.7%)	2
AEs leading to death	0	0	0	0	0	0
Drug-related AEs	5 (45.5%)	9	6 (50.0%)	10	5 (38.5%)	7
Drug-related SAEs	0	0	0	0	1 (7.7%)	2
Drug-related AEs by SOC, PT						
Cardiac disorders	0	0	0	0	1 (7.7%)	1
Bradycardia	0	0	0	0	1 (7.7%)	1
Gastrointestinal disorders	1 (9.1%)	1	4 (33.3%)	5	0	0
Nausea	0	0	4 (33.3%)	4	0	0
Vomiting	1 (9.1%)	1	1 (8.3%)	1	0	0
General disorders and administration site conditions	1 (9.1%)	1	2 (16.7%)	2	0	0
Fatigue	0	0	1 (8.3%)	1	0	0
Infusion site phlebitis	0	0	1 (8.3%)	1	0	0
Pyrexia	1 (9.1%)	1	0	0	0	0
Infections and infestations	0	0	0	0	1 (7.7%)	1
Infusion site infection	0	0	0	0	1 (7.7%)	1
Investigations	2 (18.2%)	2	1 (8.3%)	1	1 (7.7%)	1
Blood ALP increased	0	0	0	0	1 (7.7%)	1
Blood CK increased	1 (9.1%)	1	0	0	0	0
Hepatic enzyme increased	0	0	1 (8.3%)	1	0	0
LFT abnormal	1 (9.1%)	1	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	2 (15.4%)	3
Gout	0	0	0	0	1 (7.7%)	2
Hyperglycaemia	0	0	0	0	1 (7.7%)	1
Nervous system disorders	3 (27.3%)	4	2 (16.7%)	2	0	0
Cerebrovascular accident	1 (9.1%)	1	1 (8.3%)	1	0	0
Headache	1 (9.1%)	1	1 (8.3%)	1	0	0
Simple partial seizures	1 (9.1%)	1	0	0	0	0
Somnolence	1 (9.1%)	1	0	0	0	0
Skin and subcutaneous tissue disorders	1 (9.1%)	1	0	0	0	0
Rash	1 (9.1%)	1	0	0	0	0
Vascular disorders	0	0	0	0	1 (7.7%)	1
Hypotension	0	0	0	0	1 (7.7%)	1

Table 34 Adverse Events from Study 13, a Study in Japanese

	Postmarketing Clinical Study MCI186-13	
Drug-related AEs by SOC, PT	Edaravone (N = 194) n (%)	Ozagrel (N = 198) n (%)
General disorders and administration site conditions	3 (1.5%)	3 (1.5%)
Pyrexia	2 (1.0%)	2 (1.0%)
Infusion site erythema	1 (0.5%)	0
Oedema peripheral	0	1 (0.5%)
Cardiac disorders	2 (1.0%)	1 (0.5%)
Tachycardia	1 (0.5%)	0
Ventricular extrasystoles	1 (0.5%)	0
Arrhythmia	0	1 (0.5%)
Infections and infestations	2 (1.0%)	1 (0.5%)
Pyelonephritis acute	1 (0.5%)	0
Urinary tract infection	1 (0.5%)*	0
Bacteraemia	0	1 (0.5%)
Investigations	2 (1.0%)	0
Blood pressure increased	1 (0.5%)	0
Occult blood positive	1 (0.5%)	0
Metabolism and nutrition disorders	2 (1.0%)	0
Hypoglycaemia	1 (0.5%)	0
Hypokalaemia	1 (0.5%)	0
Psychiatric disorders	2 (1.0%)	1 (0.5%)
Insomnia	2 (1.0%)	1 (0.5%)
Blood and lymphatic system disorders	1 (0.5%)	0
Anaemia	1 (0.5%)	0
Nervous system disorders	1 (0.5%)	2 (1.0%)
Headache	1 (0.5%)	2 (1.0%)
Haemorrhagic cerebral infarction	0	1 (0.5%)
Tension headache	0	1 (0.5%)
Renal and urinary disorders	1 (0.5%)	1 (0.5%)
Pollakiuria	1 (0.5%)	0
Renal impairment	0	1 (0.5%)
Reproductive system and breast disorders	1 (0.5%)	0
Genital haemorrhage	1 (0.5%)	0
Respiratory, thoracic and mediastinal disorders	1 (0.5%)	1 (0.5%)
Wheezing	1 (0.5%)	1 (0.5%)
Eye disorders	0	1 (0.5%)
Conjunctival haemorrhage	0	1 (0.5%)
Vascular disorders	0	1 (0.5%)
Phlebitis	0	1 (0.5%)

7.2. Integrated Assessment of Effectiveness

In my opinion, the evidence demonstrates that the drug has effectiveness in ALS. There is not good evidence addressing the issue of duration or persistence of effect, although for a disease with a median survival of 3 years, I believe the improvements in functionality as measured by the ALSFRS and certain secondary endpoints (e.g., modified Norris Scale score) is clinically meaningful. The issue of the study patients in the ALS program all being Japanese and the bridging to the US population, I believe, is satisfactorily addressed with the evidence discussed in Section 8.1.2 of this review.

I believe Study 19 has many features that would be expected for a single study approval. It was **robustly positive**, with a P value of 0.0013 on the primary endpoint**, multi-centered**, and some of **the secondary endpoints were supportive**. The latter point is tempered by there not being a correction for multiplicity in the testing of endpoints. While post-hoc, the results from Study 16 may be considered as confirmatory evidence. This finding is weakened by virtue of the positive result being post-hoc, and some minor imbalances in the final post-hoc analysis population. On balance, I believe the applicant has provided adequate evidence of an effect of edaravone in the treatment of ALS.

8 Review of Safety

8.1. Safety Review Approach

The clinical development program of edaravone for ALS included 5 completed studies conducted in Japan: 1 Phase II study (MCI186-12) and 4 Phase III studies (MCI186-16, MCI186-17, MCI186-18, and MCI186-19). There are no ongoing clinical studies for edaravone.

The applicant grouped the studies evaluable for safety into the following sets that are described in Table 35 :

- Safety Integrated Analysis Set 1: Placebo-Controlled Studies (Cycle 1 through 6) MCI186-16, MCI186-18, and MCI186-19 [double-blind period]);
- Safety Integrated Analysis Set 2 All Edaravone (Safety Integrated Analysis Set 2: MCI186-12, MCI186-16, MCI186-17, MCI186-18, and MCI186-19);
- Safety Integrated Analysis Set 3 Continuous Long-term Edaravone (7 Cycles or More) (MCI186-16 with its extension MCI186-17 and MCI186-19).
- Safety Integrated Analysis Set 4: Placebo-Controlled Extension Period (Cycle 7 through 12) MCI186-17 and MCI186-19 [active extension period]).

Table 35 Summary of the ALS Integrated Safety Data Sets

Name of Safety Analysis Set	Objective	Treatment groups	Treatment duration:	Study number
Placebo-Controlled Studies (Cycle 1 through 6) - Safety Integrated Analysis Set 1	Randomized, placebo-controlled safety evaluation in subjects treated in double-blind study period	Placebo Edaravone	6 cycles:	MCI186-16 MCI186-18 MCI186-19 (double-blind period)
All Edaravone - Safety Integrated Analysis Set 2	Safety evaluation in all subjects treated with edaravone, as the largest actively-treated analysis set	Edaravone	6 cycles: 3 or 9 cycles: 12 cycles:	MCI186-12 MCI186-16 MCI186-18 MCI186-19 (double-blind period MCI186-17 MCI186-19 (double-blind period + active extension period)
Continuous Long-term Edaravone (7 Cycles or More) - Safety Integrated Analysis Set 3	Safety evaluation in all subjects treated with edaravone continuously from Cycle 1 through 7 or further	Edaravone	6 cycles: 9 cycles: 12 cycles:	MCI186-16 MCI186-17 MCI186-19 (double-blind period + active extension period)
Placebo-Controlled Extension Period (Cycle 7 through 12) - Safety Integrated Analysis Set 4	Placebo-controlled safety evaluation in subjects treated in Cycle 7 through 12	Edaravone–Placebo[a] Placebo–Edaravone[b] Edaravone–Edaravone[c]	6 cycles:	MCI186-17 MCI186-19 (active extension period)

[a] Edaravone group in MCI186-16 followed by placebo group in MCI186-17 (EP group).
[b] Includes placebo group in MCI186-16 followed by edaravone group in MCI186-17 (PE group) and placebo group in double-blind period of MCI186-19 followed by edaravone group in active extension period of MCI186-19 (P-E group).
[c] Includes edaravone group in MCI186-16 followed by edaravone group in MCI186-17 (EE group) and edaravone group in double-blind period of MCI186-19 followed by edaravone group in active extension period of MCI186-19 (E-E group).

Source: Summary of Clinical Safety Table 2.7.4.3.1.2-1 p.

I will focus on 3 groups from this application

- Set 1, because this will form the basis of any analyses relative to placebo. The Table of Adverse Events in Section 6 of the labeling will be derived from this Set.
- Set 2, which contains the balance of the edaravone safety data for this indication, and
- Studies from other indications, which was submitted by the applicant in Study Reports
    - Report No. MCI186-N03 Safety Specification Assessment Report: Summary of Non-Amyotrophic Lateral Sclerosis Safety Experience,
    - Report No. MCI186-N04 Safety Specification Assessment Report: Review of Clinically Significant Adverse Reactions for Determination of Risks for Edaravone.

Since vital signs and electrocardiograms were not performed in the Phase 2 and 3 studies of the ALS program, I have described results from two PK studies where edaravone was dosed in Caucasian patients. These studies are described in **Section 8.3.1 Vital Signs.**

8.1. Review of the Safety Database

8.1.1. Overall Exposure

A total of 349 patients received edaravone in the ALS clinical trial program. Among these patients, 306 patients received edaravone for at least 6 months (6 cycles), and 98 patients received edaravone for at least 12 months (12 cycles). A summary of patients completing by cycle is found in Table 36 .

Table 36 Summary of Total Treatment Cycles by Patients Receiving Edaravone (Safety Set 2)

Treatment Group	Edaravone (N=349)
No. of cycles [a]	No. of patients (%) [b]
1	349 (100.0)
2	345 (98.9)
3	333 (95.4)
4	328 (94.0)
5	319 (91.4)
6	306 (87.7)
7	229 (65.6)
8	222 (63.6)
9	219 (62.8)
10	105 (30.1)
11	102 (29.2)
12	98 (28.1)
13	44 (12.6)
14	41 (11.7)
15	37 (10.6)

Note: (a) Total number of cycles in which patients received at least one treatment.
(b) Cummulative number and percent of total patients from Cycle 1.
(c) Each cycle consists of 28 days. Cycle 1: administration for 14 consecutive days, followed by a drug-free period of 2 weeks, Cycle 2 and after; administration for a total of 10 days per 2 weeks, followed by a drug-free period of 2 weeks.

Summary of Clinical Safety, Table 2.7.4.3.2.2-1, p.33/164

During the placebo-controlled studies in ALS (Cycle 1 through 6), 184 patients received edaravone and 184 patients received placebo. In the edaravone group, 94.6% of the patients received 6 cycles of edaravone. 169 (91.8%) of patients receiving edaravone completed 6 cycles and 15 (8.2%) discontinued treatment in Cycles 1-6. This is in contrast to 162 patients (88%) on placebo completing and 22 (12%) discontinuing.

Reasons for discontinuing were balanced between treatment groups, though the number of patients mentioned to have "requested to discontinue study without further explanation was proportionately high (Table 37).

Table 37 Reasons for Discontinuation of Patients (Safety Analysis Set 1)

Reasons for Study Discontinuation	MCI186-16 Placebo (N = 104)	MCI186-16 Edaravone (N = 102)	MCI186-18 Placebo (N = 12)	MCI186-18 Edaravone (N = 13)	MCI186-19 (double-blind period) Placebo (N = 68)	MCI186-19 (double-blind period) Edaravone (N = 69)
Subject requested to discontinue study	5	5	0	2	2	0
Study continuation was judged difficult due to SAEs or worsening of primary disease	-	-	-	-	-	-
Due to occurrence of AEs, investigator (subinvestigator) judged it difficult to continue study.	6	3	0	1	2	0
Subject had to undergo tracheostomy	2	1	0	0	1	1
Pregnancy was revealed	0	0	0	0	-	-
Deviation from study protocol became inevitable, and study continuation was considered difficult	1	0	0	0	-	-
Creatinine clearance ≤50 mL/min	0	0	0	0	0	0
Subject was disqualified as study participant after study start	0	0	0	0	0	0
By subject's own reasons, study continuation became impossible	0	0	0	1	-	-
It was found that subject was clearly ineligible to participate in study.	-	-	-	-	-	-
Subject had to use respiratory assist device all day.	-	-	-	-	1	0
Due to worsening of primary disease, investigator (subinvestigator) judged it unreasonable to continue study.	-	-	-	-	0	0
Subject underwent spinal operation for cervical spondylosis or intervertebral disk hernia.	-	-	-	-	0	0
%FVC ≤ 50% and $PaCO_2$ of blood gas ≥45 mmHg.	-	-	-	-	1	1
Others, investigator or subinvestigator judged it inappropriate/impossible to continue study.	0	0	0	0	1	0
Total no. of discontinued subjects	14	9	0	4	8	2

Source: ISS Table 6.1.4.

Source: Summary of Clinical Safety 2.7.4.3.2.1.-3, p.32/164

Table 38, which describes data from the active treatment arms of edaravone studies, may be considered in conjunction with Table 37 to describe the whole population receiving edaravone. Discontinuations were for expected reasons considering the disease natural history.

Table 38 Reasons for Discontinuation in Placebo Controlled Extension Periods of Edaravone Trials (Safety Set 4)

Reasons for Study Discontinuation	Study No. / Treatment group				
	MCI186-17			MCI186-19 (active extension period)	
	EP group (N = 45)	PE group (N = 88)	EE group (N = 48)	P-E group (N = 58)	E-E group (N = 65)
Subject requested to discontinue study	2	5	1	7	6
Study continuation was judged difficult due to SAEs or worsening of primary disease	-	-	-	-	-
Due to occurrence of AEs, investigator (subinvestigator) judged it difficult to continue study.	2	2	1	2	1
Subject had to undergo tracheostomy	0	5	2	0	0
Pregnancy was revealed	0	0	0	-	-
Deviation from study protocol became inevitable, and study continuation was considered difficult	0	0	0	-	-
Creatinine clearance ≤50 mL/min	0	0	0	0	0
Subject was disqualified as study participant after study start	0	0	0	0	0
By subject's own reasons, study continuation became impossible	0	0	0	-	-
It was found that subject was clearly ineligible to participate in study.	-	-	-	-	-
Subject had to use respiratory assist device all day.	-	-	-	3	0
Due to worsening of primary disease, investigator (subinvestigator) judged it unreasonable to continue study.	-	-	-	0	1
Subject underwent spinal operation for cervical spondylosis or intervertebral disk hernia.	-	-	-	0	0
%FVC ≤ 50% and $PaCO_2$ of blood gas ≥45 mmHg.	-	-	-	6	4
Others, investigator or subinvestigator judged it inappropriate/impossible to continue study.	0	1	0	0	0
Total no. of discontinued subjects	4	13	4	18	12

Source: ISS Table 6.1.5.

Source: Summary of Clinical Safety, Table 2.7.4.3.2.4-3, p 35/164

8.1.2. **Relevant characteristics of the safety population:**

Demographics for patients entering into edaravone placebo-controlled trials as well as those entering other treatment phases were balanced between treatment groups.

Table 39 Demographics and Baseline Characteristics of Patients in Safety Set 1

Parameter			Placebo (N = 184)		Edaravone (N = 184)	
Gender		Male, n (%)	116	(63.0)	109	(59.2)
		Female, n (%)	68	(37.0)	75	(40.8)
Age (years)		No. of subjects	184		184	
		Mean (SD)	58.7 (9.9)		58.8 (9.8)	
		Min, Max	28, 75		29, 75	
		Median	60.0		60.0	
		< 65 years, n (%)	127	(69.0)	131	(71.2)
		≥ 65 years, n (%)	57	(31.0)	53	(28.8)
Body weight (kg)		No. of subjects	184		184	
		Mean (SD)	58.3 (10.9)		57.8 (10.7)	
		Min, Max	37, 109		35, 105	
		Median	57.0		56.0	
Disease duration (years)		No. of subjects	184		184	
		Mean (SD)	1.26 (0.62)		1.34 (0.59)	
		Min, Max	0.2, 3.0		0.3, 2.9	
		Median	1.20		1.30	
		< 1 year, n (%)	71	(38.6)	57	(31.0)
		≥1 year, n (%)	113	(61.4)	127	(69.0)
Initial symptoms		Bulbar symptoms, n (%)	34	(18.5)	37	(20.1)
		Limb symptoms, n (%)	150	(81.5)	147	(79.9)
ALS diagnosis		Sporadic, n (%)	177	(96.2)	182	(98.9)
		Familial, n (%)	7	(3.8)	2	(1.1)
El Escorial Revised Airlie House Diagnostic Criteria		Definite ALS, n (%)	50	(27.2)	64	(34.8)
		Probable ALS, n (%)	103	(56.0)	97	(52.7)
		Probable ALS - Laboratory supported, n (%)	30	(16.3)	22	(12.0)
		Possible ALS, n (%)	1	(0.5)	0	(0.0)
		Suspected ALS, n (%)	0	(0.0)	1	(0.5)
		Not rated, n (%)	0	(0.0)	0	(0.0)
ALS Severity Grade		Grade 1, n (%)	56	(30.4)	58	(31.5)
		Grade 2, n (%)	116	(63.0)	113	(61.4)
		Grade 3, n (%)	12	(6.5)	13	(7.1)
ALSFRS-R Score	Pre-registration	No. of subjects	184		184	
		Mean (SD)	43.0 (3.0)		42.4 (3.9)	
		Min, Max	29, 48		25, 48	
		Median	43.0		43.0	
	At baseline in Cycle 1	No. of subjects	184		184	
		Mean (SD)	41.0 (3.2)		40.5 (4.0)	
		Min, Max	28, 47		23, 47	
		Median	42.0		41.0	

Source: Summary of Clinical Safety, Table 2.7.4.3.3.1-1, p. 37/164

8.1.3. Adequacy of the safety database:

The quality of the data in the database is good and interpretable. The applicant's summary and critique of the postmarketing data is similarly quite good. The program lacks long term controlled data; however, in the absence of any strong signals from the trial database, standard postmarketing surveillance is considered adequate.

8.2. Adequacy of applicant's Clinical Safety Assessments

8.2.1. Issues Regarding Data Integrity and Submission Quality

8.2.2. Categorization of Adverse Events

For the integrated analyses, MedDRA/J version 17 was used, which was the version in use at the time of the database lock for the last completed clinical study (MCI186-19).

For patients who participated in both treatment periods of MCI186-19 (double-blind period and active extension period) or who participated in MCI186-17 as an extension of MCI186-16, AEs that occurred on or after Day 1 of dosing in the subsequent period or extension period were not included in Placebo-Controlled Studies (Cycle 1 through 6) - Safety Integrated Analysis Set 1. For these same patients, AEs that occurred before Day 1 of Cycle 7 were not included in Placebo-Controlled Extension Period (Cycle 7 through 12) - Safety Integrated Analysis Set 4.

In 4 of the 5 ALS studies (i.e., MCI186-12, MCI186-16, MCI186-17, and MCI186-18), relationship of AEs to the IMP was determined by investigators (or subinvestigators) using 4 categories of causality: none/not related, remote/unlikely related, possible/possibly related, or probable/probably related. In these 4 studies, AEs evaluated as possibly related or probably related were summarized as "drug-related AEs." In the 5th study (Study MCI186-19), relationship of AEs to the IMP was determined using 2 categories of causality: "a reasonable possibility" or "not a reasonable possibility"; in this study, AEs evaluated as "a reasonable possibility" were summarized as "drug-related AEs." For the purpose of this integrated analysis, AEs assigned as possibly related or probably related from the first 4 studies and AEs assigned as "a reasonable possibility" from the 5th study were classified under the relationship assessment of "Reasonable possibility"; AEs assigned as not related or unlikely related from the first 4 studies and AEs assigned as "Not a reasonable possibility" from the 5th study were classified under the relationship assessment of "No reasonable possibility."

For tabulations of AEs by severity, analyses were based on the investigator's attribution of severity grade. Pre-specified definitions of severity grades (mild, moderate, severe) were provided to the investigators in the protocols. In all 5 studies (Studies MCI186-12, MCI186-16, MCI186-17, MCI186-18, and MCI186-19), the severity of AEs was evaluated by using 3 categories: "Mild (activities of daily living are not disturbed)," "Moderate (activities of daily living are disturbed by the symptom to some extent)," and "Severe (activities of daily living are disturbed by the symptom to a great large extent)."

8.3. Safety Results

8.3.1. Deaths

In placebo-controlled studies (Cycle 1 through 6) - Safety Integrated Analysis Set 1, the incidence of treatment-emergent death was 1.1% (2/184) patients in the placebo group and 2.2% (4/184) patients in the edaravone group. All 4 patients died of a respiratory disorder; 5 patients were from Study 16, 1 was from Study 18 (**Table 40**).

Table 40 Deaths in Placebo-Controlled Portions of Edaravone Trials (Safety Set 1)

Clinical Study Subject No. Treatment Group	Gender/ Age	Preferred Term(s)	Date of First Dose/ Date of Last Dose	Date of Death (Cycle No.)	Severity	Causal Relationship
MCI186-16 0408 Placebo	M/64	Respiratory failure	16-Mar-2007/ 06-Jul-2007	(b) (6)	Severe	Not a reasonable possibility
MCI186-16 1607 Placebo	M/64	Respiratory failure	05-Feb-2008 10-Apr-2008		Severe	Not a reasonable possibility
MCI186-16 0304 Edaravone	M/57	Respiratory disorder	17-Jan-2007/ 24-Apr-2007		Severe	Not a reasonable possibility
MCI186-16 0407 Edaravone	F/57	Respiratory failure	28-Feb-2007/ 26-Jul-2007		Severe	Not a reasonable possibility
MCI186-16 1309 Edaravone	M/70	Respiratory disorder	31-Oct-2007/ 29-Feb-2008		Severe	Not a reasonable possibility
MCI186-18 0502 Edaravone	M/52	Respiratory failure	08-Dec-2007/ 08-May-2008		Severe	Not a reasonable possibility

MedDRA version 17.0. All subjects received edaravone at dosage of 60 mg/day.
[a] The onset of the fatal event for this subject occurred in Cycle 4, but subject's death occurred in Cycle 6.

Source: Table 2.7.4.4.1.3-2, p 77/164

Medical Officer's Comments: Having reviewed the narratives, I am in agreement with the applicant that disease progression is most likely the cause of the cases of Death.

8.1. Serious Adverse Events

In Placebo-Controlled Studies (Cycle 1 through 6) - Safety Integrated Analysis Set 1, the incidence of treatment-emergent SAEs was 22.3% (41/184) patients in the placebo group and 17.4% (32/184) patients in the edaravone group.

Table 41 Incidence of Treatment-emergent SAEs in Placebo-Controlled Portion of Edaravone Studies by SOC and PT (Safety Set 1)

SOC PT	Placebo (N = 184) n	(%)	Edaravone (N = 184) n	(%)
Any SAE[a]	41	(22.3)	32	(17.4)
Infections and infestations	2	(1.1)	3	(1.6)
Cellulitis	1	(0.5)	0	(0.0)
Gastroenteritis	0	(0.0)	1	(0.5)
Pneumonia	0	(0.0)	1	(0.5)
Bacterial infection	1	(0.5)	1	(0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.5)	0	(0.0)
Gastric cancer	1	(0.5)	0	(0.0)
Metabolism and nutrition disorders	1	(0.5)	0	(0.0)
Hypoproteinaemia	1	(0.5)	0	(0.0)
Psychiatric disorders	3	(1.6)	0	(0.0)
Anxiety	1	(0.5)	0	(0.0)
Depression	2	(1.1)	0	(0.0)
Nervous system disorders	3	(1.6)	1	(0.5)
Dyslalia	2	(1.1)	1	(0.5)
Speech disorder	1	(0.5)	0	(0.0)
Ear and labyrinth disorders	1	(0.5)	0	(0.0)
Vertigo positional	1	(0.5)	0	(0.0)
Vascular disorders	1	(0.5)	0	(0.0)
Pelvic venous thrombosis	1	(0.5)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	12	(6.5)	11	(6.0)
Aspiration	1	(0.5)	0	(0.0)
Dyspnoea	1	(0.5)	3	(1.6)
Haemoptysis	1	(0.5)	0	(0.0)
Pneumonia aspiration	3	(1.6)	0	(0.0)
Respiratory disorder	2	(1.1)	6	(3.3)
Respiratory failure	5	(2.7)	2	(1.1)
Sputum retention	0	(0.0)	1	(0.5)
Gastrointestinal disorders	21	(11.4)	19	(10.3)
Abdominal pain	0	(0.0)	1	(0.5)
Ascites	1	(0.5)	0	(0.0)
Colitis ischaemic	0	(0.0)	1	(0.5)
Dysphagia	19	(10.3)	18	(9.8)
Lower gastrointestinal haemorrhage	1	(0.5)	0	(0.0)
Hepatobiliary disorders	1	(0.5)	0	(0.0)
Drug-induced liver injury	1	(0.5)	0	(0.0)
Musculoskeletal and connective tissue disorders	7	(3.8)	4	(2.2)
Mastication disorder	1	(0.5)	0	(0.0)
Muscle spasms	1	(0.5)	0	(0.0)
Muscular weakness	1	(0.5)	1	(0.5)
Musculoskeletal disorder	5	(2.7)	4	(2.2)
General disorders and administration site conditions	3	(1.6)	5	(2.7)
Gait disturbance	2	(1.1)	3	(1.6)
Oedema peripheral	1	(0.5)	0	(0.0)
Abasia	0	(0.0)	2	(1.1)
Injury, poisoning and procedural complications	2	(1.1)	0	(0.0)
Subdural haematoma	1	(0.5)	0	(0.0)
Contusion	1	(0.5)	0	(0.0)

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

[a] Count for all subjects who had at least 1 treatment emergent SAE.

Source: Table 2.7.4.4.1.4-1, pp. 88/164

Medical Officer's Comments: The incidence of SAEs was generally low on treatment. As with the analysis of cases of Death, most SAEs seemed related to disease progression.

8.2. Dropouts and/or Discontinuations Due to Adverse Effects

In the placebo-controlled portion of edaravone studies (Safety Set 1), the edaravone arm (4 (2.2%) had slightly fewer AEs leading to discontinuation than the placebo arm (10 (5.4%)). None of the AEs were imbalanced with a greateramount typically in the placebo arm.

Table 42 Incidence of AEs that led to discontinuation (Safety Set 1)

SOC PT	Placebo (N=184) n	(%)	Edaravone (N=184) n	(%)
Any AE[a]	10	(5.4)	4	(2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.5)	0	(0.0)
Gastric cancer	1	(0.5)	0	(0.0)
Psychiatric disorders	1	(0.5)	0	(0.0)
Depression	1	(0.5)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	5	(2.7)	3	(1.6)
Respiratory disorder	1	(0.5)	1	(0.5)
Respiratory failure	4	(2.2)	2	(1.1)
Hepatobiliary disorders	1	(0.5)	0	(0.0)
Hepatic function abnormal	1	(0.5)	0	(0.0)
Skin and subcutaneous tissue disorders	2	(1.1)	1	(0.5)
Drug eruption	1	(0.5)	0	(0.0)
Rash	1	(0.5)	0	(0.0)
Toxic skin eruption	0	(0.0)	1	(0.5)

MedDRA version 17.0. A subject reporting more than 1 TEAE for a particular PT or SOC is counted only once for that PT or SOC.
[a] Count for all subjects who had at least 1 TEAE that led to discontinuation of IMP.
Source: ISS Table 6.11.1.

Source: Summary of Clinical Safety, Table 2.7.4.4.1.5-1, p. 96/164

8.2.1. Significant Adverse Events

Adverse events with the intensity of Severe were generally balanced between treatment groups (edaravone: 22 (12%) vs. PBO: (28 (15.2%)) in the placebo-controlled portions of edaravone studies (Safety Set 1). Generally, when the incidence of Severe AEs occurred at an intensity over 1% in the edaravone arm (e.g., Dysphagia, Musculoskeletal disorder) the incidence was less than that of the PBO arm, with the exception of Gait disturbance (edaravone: 10 (5.4%) vs. PBO: (5 (2.7%))

Table 43 Incidence of TEAEs Occurring in at Least 2% of Patients by Severity in Placebo-Controlled Studies (Safety Set 1)

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

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

Source: Summary of Clinical Safety, Table 2.7.4.4.1.5-3, p. 99/164

Medical Officer's Comments: The incidence of severe AEs was low, particularly those occurring at a rate greater than placebo. Gait Disturbance is the only one that stands out; however, the small numbers of patients tested and the contribution of the underlying disease confounds accurate attribution of causality.

8.2.2. Treatment Emergent Adverse Events and Adverse Reactions

Table 44 demonstrates the AEs that occurred with an incidence of at least 2% and at a frequency greater than placebo in the Safety Set 1. Most of these were mild and resolved.

Table 44 Incidence of TEAEs Occurring in at Least 2% of Patients in the Pooled Edaravone Group and Greater than Placebo Pooled in Placebo-Controlled Portions of Edaravone Studies (Safety Set 1)

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

MedDRA version 17.0. A subject reporting more than 1 TEAE for a particular PT or SOC is counted only once for that PT or SOC. Includes TEAEs with an incidence ≥ 2% in the pooled edaravone group and greater than the pooled placebo group.

Summary of Clinical Safety, Table 2.7.4.4.1.2-2, p. 48/164

Medical Officer's Comment and Analyses – I checked the coding and percentages reported in Table 44 and concur with the applicant's analysis. It is important to note that this includes patients in Studies 16 and 18 as well as 19 so this population is different, namely some more advanced in disease than the efficacy ITT full analysis group.

8.3. Laboratory Findings

Applicant's Reporting Strategy

Abnormalities that occurred more than 2 weeks after the last dose of study medication were excluded from the summary tables. For patients who participated in more than 1 period of treatment (e.g., extension period), abnormalities that occurred after Day 1 of dosing in a subsequent phase (e.g., an extension period) were excluded from the summaries of the first period.

Table 45 Applicant Criteria for Clinically Significant Laboratory Values

Laboratory Tests	Criteria
Chemistry[a]	
AST	≥ 3 x ULN
ALT	≥ 3 x ULN
ALP	> 400U/L
LDH	≥ 3 x ULN
BUN	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Uric acid	
Male	> 10.0 mg/dL
Female	> 8.0 mg/dL
T-Bil	> 2.0 mg/dL
CK	≥ 3 x ULN
Chloride (low)	≤ 90 mEq/L
Chloride (high)	≥ 118 mEq/L
Potassium (low)	< 3.0 mmol/L
Potassium (high)	> 5.5mmol/L
Sodium (low)	< 130mmol/L
Sodium (high)	≥ 150 mmol/L
Calcium (low)	< 7.0 mg/dL
Calcium (high)	≥ 12 mg/dL
Hematology[b]	
Hematocrit	
Male	37% and decrease of ≥ 3 percentage points from baseline
Female	32% and decrease of ≥ 3 percentage points from baseline
Hemoglobin	
Male	≤ 11.5 g/dL
Female	≤ 9.5 g/dL
WBC (low)	≤ 2800/mm^3
WBC (high)	≥ 16,000/mm^3
Platelet count (low)	≤ 100,000/mm^3
Platelet count (high)	≥ 700,000/mm^3
Urinalysis[c]	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units

[a] Clinical chemistry criteria as defined in "Reviewer Guidance, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review" U.S. FDA (February 2005).[1]
[b] Clinical hematology as defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," U.S. FDA (February 1987).[2]
[c] Criteria determined by Sponsor.
Source: Integrated Summary of Safety Statistical Analysis Plan, 2016.

The incidence of 'clinically relevant' serum chemistry measurements were generally similar between placebo and edaravone, the greatest imbalance being with BUN (criteria ≥ 30 mg/dL) where the edaravone arm (N=184) had 3 cases (1.6%) and the placebo (N=184) had zero cases.

The following

- Chemistry
  - Placebo-Controlled Phase

- **BUN ≥ 30mg/dL** – E (1.6%), P (0%)

- Active Treatment Phase
  - **AP ≤ 400U/L at baseline to > 400 U/L** – E-P (2.2%), P-E (3.4%), E-E (2.7%)
  - **Cl ≤ 90U/mEq/L** – E-P (0%), P-E (3.4%), E-E (1.8%)
  - **Potassium < 5.5 mmol/L to > 5.5 mmol/L** – E-P (0%), P-E (2.7%), E-E (1.8%)

- Hematology
  - Placebo-Controlled Phase
    - **Platelet Count**– E (2.7) P (0%)
  - Active Treatment Phase
    - **Hematocrit≤ 37% (M) or ≤ 32% (F) and - ≥ 3% drop** – E-P (11.1%), P-E (21.2%), E-E (19.5%)
    - **Hemoglobin ≤ 11.5 (M) or 9.5 g/dL (F) –** E-P (2.3%), P-E (3.5%), E-E (5.4%)
    - **WBC ≥ 2800 to ≤ 2800/mm^3 –** E-P (0%), P-E (3.4%), E-E (1.8%)

8.3.1. Vital Signs

The ALS development program did not test vital signs during the Phase 2 and 3 studies. Several of the clinical pharmacology studies provided analysis of a limited number of vital signs, including systolic (SYS) and diastolic (DIA) blood pressure and pulse (HR). The MCI186-EO1 and –EO2 studies were performed in Europe enrolling Caucasians, so these data are likely the most relevant.

Study –EO1 enrolled twenty four volunteers, ten who received 0.6 mg/kg of MCl-186, ten that received 1.8 mg/kg of MCl-186, and four that received placebo; two patients received placebo at each dose level. Systolic and diastolic blood pressure [mmHg], pulse rate [beats/min] and oral body temperature [°C] were measured by trained and authorized staff of (b) (4) at the following study times:

- during the pre-study examination;
- Pre-dose (within 60 minutes prior to infusion start)
- 0.5h, 1 h, 2h, 3h, 4h, 6h, 12h, 24h, 48h and at the post-study examination.

Blood pressure and pulse rate were measured in supine position after 5 minutes resting. The body temperature was measured sublingually using a digital thermometer.

Study –EO2 Fourteen patients were treated in this study; ten patients (five males and five females) received edaravone and four patients (two males and two females) received placebo. The treatment groups were as follows: Treatment group 1 received a 0.1 mg/kg bolus (3 min) of MCI-186, followed by a 0.25 mg/kg/h infusion over 23h57min. Treatment group 2 received a 0.2 mg/kg bolus (3 min) of MCI-186, followed by a 0.50 mg/kg/h infusion over 23h57min. Treatment group 3 was planned to receive a 0.3 mg/kg bolus (3 min) of MCI-186, followed by a 0.75 mg/kg/h infusion over ~ 24 hours. However, based on interim PK analysis, it was decided to change the dose of treatment group 3 to a 0.05 mg/kg bolus (3 min) of MCI-186, followed by a 0.125 mg/kg/h infusion over 23h57min. As a reference treatment, 4 patients per group received a

bolus (3 min) of matching placebo, followed by an infusion over ~ 24 hours. Mean age of patients in the four treatment cohorts ranged from 58.7 to 63.6.

Blood pressure, pulse rate and oral body temperature were assessed at screening, at Day -1, Day 1 to Day 3 (pre-dose and 30 min, 1h, 2h, 4h, 8h, 12h, 16h, 20h, 24h, 30h, 36h, 42h and 48h after start of the infusion) and at the one (1) week follow-up visit.

With one exception, vital signs did not generally differ between groups and did not contain clinically notable results. In study EO2, the pulse rate was higher in Group 2 than Group 1 ()

8.3.2. **Electrocardiograms (ECGs)**

ECGs were not measured in the Phase 2 and 3 studies of the ALS program; however 5 of the PK studies contained ECGs. Two of them, -EO1 and EO2, were conducted in Caucasian patients and are described in the previous section on Vital signs.

No clinically significant changes in ECG intervals (PR, ORS, QTc) or overall morphology from pre- to post-dose were observed. For all treatments, arithmetic means of PR-time, ORS-time and QTc-time were within the normal limits (PR-time: 110 - 210 msec, ORS-time: 70 - 110 msec and QTc-time: < 450 msec (males) and < 470 msec (females)) and showed only minor variations.

8.3.2.1. QT

- FDA Interdisciplinary Review Team for QT Studies reviewed the submission and provided comments on the potential for Edaravone to cause QT prolongation. They noted that the sole study containing ECG assessments, MCI-186-02, a randomized, Phase I, double-blind, placebo-controlled, ascending IV dose study in 46 patients cannot be used to exclude small effects (10 ms threshold) as per the ICH E14 and ICH E14 Q&A (R3) guidelines. This study did not evaluate directly the intended therapeutic dose (60 mg IV infusion in 60 min once daily). But, the 24-hour infusion of highest dose group of 0.2 mg/kg bolus +0.5 mg/kg/h infusion in this study reached a similar end of infusion plasma concentration of edaravone (1164 ng/mL) as the estimated Cmax after proposed therapeutic dosing of 60 mg/60 min IV infusion (Cmax after 60 mg/60 min IV infusion of edaravone is estimated as1049 ng/mL according to Population-PK simulations).

- They noted several limitations of this study which make it uninterpretable for excluding small QTc effects (<10 ms):

- There was no supratherapeutic dose/exposure studied; therefore, the QTc effects at the high clinical exposure scenario have not been characterized. The primary route of elimination for the drug and its metabolites is renal route. Thus renal impairment likely constitutes the worst case high exposure scenario for the same therapeutic dose. There is no PK information available for quantifying this high exposure scenario and there was no supratherapeutic dose studied to cover such exposures.

- ECG quality and ECG/PK assessment is not adequate. Single 12-lead ECGs (no replicates) were measured at baseline pre-dose and at different time points. The matched ECG/PK sampling post end-of-infusion was not adequate to evaluate the possible hysteresis effect of concentration on response.
- ECG assay sensitivity was not established in the study.
- The study did not have any higher dose to evaluate effects at multiple-fold (at least 2-fold) of clinically relevant highest exposure to waive the requirement of a positive control as per ICH E14 Q&A (R3) guidance phase studies.

The QTIRT recommends that the sponsor conducts a TQT study for this product as a PMR to exclude small QT prolongation effects (10 ms threshold). The sponsor should submit the protocol for our review and comment. No labeling is proposed currently by the sponsor for QT effects and the QTIRT recommend not having any labeling language for QT effects based on this study.

8.3.3. **Immunogenicity**

Immunogenicity was not assed as part of this submission. Considering edaravone is a small molecule and did not exhibit signs of immunogenicity in the placebo controlled study, such as hypersensitivity and loss of effect, I do not think such studies are warranted at this time. This may be monitored by standard postmarketing surveillance.

8.4. **Safety Analyses by Demographic Subgroups**

- Healthy Volunteers
  - A total of 133 healthy volunteers (edaravone: 100, placebo: 33) were analyzed for safety in 5 studies [1 Phase I study in Japan (MCI186-01), 2 Phase I studies in Europe (MCI186-E01, MCI186-E02), and 2 clinical pharmacology studies in Japan (MCI186-10, MCI186-14)].
  - No safety signals were observed in the 5 studies. No SAEs, AEs resulting in discontinuation, deaths, or other significant AEs were reported in these studies.
  - Incidences and types of treatment-emergent AEs and drug-related AEs were similar between the placebo and edaravone groups.
  - There were no clinically significant changes in laboratory parameters, vital signs, electrocardiograms (ECGs), physical examination, and neurological assessments.
  - No patients administered edaravone experienced AEs or clinically significant laboratory abnormalities associated with hepatic or renal dysfunction.
  - No safety concerns related to hepatic or renal dysfunction or hypersensitivity arose from these studies.
- Gender
  - The TEAEs that were reported at a higher incidence (i.e., +2%) among females in the edaravone group (compared to females in the placebo group) that occurred at comparable or lower incidences (edaravone versus placebo) among males included Upper respiratory tract infection, Headache, Nausea, Hepatic steatosis, Erythema, Rash, Myalgia, Neck pain, Excoriation, and Procedural pain. The most frequently reported PT among females in the edaravone group was Contusion (21.3%), which was higher than the incidence

among females in the placebo group (11.8%) and higher than the incidences among males (10.1% in the edaravone group and 6.9% in the placebo group).

– The TEAEs that were reported at a higher incidence (i.e., +2%) among males in the edaravone group (compared to males in the placebo group) that occurred at comparable or lower incidences (edaravone versus placebo) among females included Nasopharyngitis, Upper respiratory tract inflammation, Dermatitis contact, and Glucose urine present. The most frequently reported PTs among males in the edaravone group was Nasopharyngitis (17.4%), which was higher than the incidence among males in the placebo group (14.7%); among females this event was reported at a lower incidence in the edaravone group (10.7% in the edaravone group and 17.6% in the placebo group).
– For the 7 TEAEs with a higher incidence (i.e., +2%) in the edaravone group compared to the placebo group (Headache, Gait disturbance, Dermatitis contact, Eczema, Respiratory disorder, Glucose urine present, and Contusion), no clear differences by gender were observed across the 2 treatment groups.
– In the Active Treatment period of Study 19 (Group 4), four of the 10 TEAEs (Catheter site infection, Respiratory disorder, Pyrexia, and Dermatitis contact) had higher incidences among females in the Edaravone–Edaravone group compared to males (and by high margins, particularly Respiratory disorder): Respiratory disorder (12.0% among females versus 1.6% among males), Pyrexia (4.0% among females versus 1.6% among males), and Dermatitis contact (4.0% among females versus 1.6% among males). The remaining 3 TEAEs (Gastritis, Musculoskeletal disorder, and Nocturia) had higher incidences among males in the Edaravone-Edaravone group, compared to females (and by high margins): Gastritis (6.3% among males versus 2.0% among females), Musculoskeletal disorder (12.7% among males versus 6.0% among females), and Nocturia (4.8% among males versus 0.0% among females).

• Age

– Adverse events that occurred in the double blind part of Study 19 at a higher frequency (+5%) in those ≥ 65 (N = 53 vs < 65 N = 131)) and in a greater frequency than placebo (N≥ 65 = 57) were (%≥ 65 vs. PBO; % <65) Nasopharyngitis (18.9% vs. 10.5; 13.0), Dysphagia (20.8% vs. 19.3; 5.3%), Back pain (7.5% vs. 1.8%; 2.3%).
– No specific trends were noted in the Active treatment part of Study 19. In the Edaravone – Edaravone group, only 2 of the 10 TEAEs had higher incidences among elderly patients: Speech disorder and Eczema.

8.5. Safety in the Postmarket Setting

8.5.1. Safety Concerns Identified Through Postmarket or Non-ALS Experience

2.7.4.8 Postmarketing Data and Data from Indications outside of ALS

Amyotrophic Lateral Sclerosis

• Approximately 1200 ALS patients have been exposed to edaravone since the approval in Japan in December 2015 to June 2015. Reported serious cases were anemia (1 case), asthma (1 case), respiratory failure (2 cases), and blood creatine (phospho)kinase (CK) increased (1 case); No new safety signals have been identified from ALS postmarketing experience.

Acute Ischemic Stroke

- The applicant provided a summary of the 5 Clinical AIS studies [1 Phase I study in Japan (MCI186-01), 2 Phase I studies in Europe (MCI186-E01, MCI186-E02), and 2 clinical pharmacology studies in Japan (MCI186-10, MCI186-14)]. A total of 786 patients with AIS were analyzed for safety in 5 Japanese studies. Edaravone was also evaluated in > 4000 patients with AIS in Japanese postmarketing studies.
  - In the 5 Japanese AIS studies (edaravone: 569, placebo: 125), the overall incidence of drug-related AEs (based on investigator attribution) was 4.6%. In the Phase III study, incidences of drug-related AEs, hepatic function disorder, and deaths were similar between the 2 treatment groups (edaravone versus placebo): 7.2% versus 11.2% for drug-related AEs; 3.2% versus 5.6% for hepatic function disorder; 3.4% versus 5.5% for death. Incidences of drug-related AEs were similar among elderly patients versus non-elderly patients (4.0% versus 5.5%).
- In a postmarketing study, the Drug Use-Results Survey (safety analysis set: 3882 patients), drug-related AEs developed in 11.1% (431/3882 patients). Incidences of drug-related AEs were higher in the presence (16.8%) than in the absence (10.6%) of hepatic function disorder, and were higher in the presence (23.9%) than in the absence (10.4%) of renal impairment. No significant difference was noted in the incidence of drug-related AEs in the elderly (10.9%) versus non-elderly (11.7%). Overall, there were no safety concerns in a Special Drug Use-Results Survey in patients with pediatric cerebral infarction (safety analysis set: 118 patients). Incidence of drug-related AEs was 4.2%, which was lower than that observed in the Drug Use-Results Survey described above.
- As of the cutoff for this assessment (31 December 2015), approximately 1.7 million AIS patients have been exposed to edaravone as postmarketing experience. A total of 2451 AEs (2205 ADRs) have been reported spontaneously among AIS patients in Japan for commercially available edaravone. The System Organ Classes (SOCs) with the most frequently reported ADRs among AIS patients included Renal and urinary disorders, Hepatobiliary disorders, Investigations, and Skin and subcutaneous tissue disorders.

Subarachnoid Hemorrhage

- A total of 585 patients with SAH were analyzed for safety in 3 Japanese studies including 2 Phase II studies (MCI186-04 and MCI186-08) and 1 Phase III study (MCI186-11), including 367 patients treated with edaravone.
  - In the 2 placebo-controlled SAH studies, no significant difference in incidences of drug-related AEs and SAEs was observed between the edaravone group and the placebo group. In laboratory tests and physical examination, no change in characteristics to the edaravone group was observed in comparison with the placebo group.

- As a matter of routine based on local practice, the applicant investigated the incidence of the following events considered to be of clinical significance:
  - Fulminant hepatitis, hepatic dysfunction, jaundice;
  - Acute renal failure (ARF), nephrotic syndrome;
  - Shock, anaphylactoid reaction;
  - Thrombocytopenia;
  - Granulocytopenia;
  - Rhabdomyolysis;

- Disseminated intravascular coagulation (DIC);
- Acute lung injury (ALI).

These analyses are captured in the applicant's summary, MCI186-N04 Study Report Safety Specification Assessment Report: Review of Clinically Significant Adverse Reactions for Determination of Risks for Edaravone MCI-186 (Edaravone) Injection. This report can be distilled to the following findings:

- Data from controlled studies in ALS, AIS, and SAH suggest there are no signals in these conditions.
- Analyses of case series in the literature on hepatic disorders, renal failure, and anaphylactic reactions suggested that all cases of interest were confounded. Analysis of postmarketing of cases for all disorders evaluated EXCEPT anaphylactic reactions suggested all had confounding medical or concomitant issues. In the series for anaphylactic reactions, there were 10 cases that both the applicant and I believe, based on their narratives, could be attributable to, or at least potentially exacerbated by edaravone.

Anaphylactic Shock, Anaphylactic Reactions, Anaphylactoid Reactions, and Hypersensitivity in the Postmarketing Edaravone Data

One subject in All Edaravone - Safety Integrated Analysis Set 2 (1/349, 0.3%) experienced a SAE of shock (respiratory distress on Day 233 of treatment, shock on Day 240). The AE of Shock occurred 8 days after the subject's last dose. The shock resolved (event duration: 2 days); respiratory distress was not reported as resolved. The Investigator deemed the events had no reasonable possibility of an association with edaravone:

A search of ARISg, the Mitsubishi Tanabe Pharma Corporation internal global safety database was conducted in order to identify potential cases of ***shock/anaphylactoid reaction***, using MedDRA (version 18.1) *SMQ Anaphylactic/ Level 2 SMQ anaphylactoid shock conditions*, and a cutoff date of 25 December 2015. As of that date, the search retrieved a total of 358 cases in ARISg that met the search criteria. The 358 retrieved cases included 288 spontaneous reports, 60 reports from survey studies, 2 literature reports, and 8 authority reports. Cases were medically evaluated for sufficient clinical and diagnostic details to allow further assessment (i.e., whether the event course and/or medical diagnosis is confirmed or appropriate for the clinically significant ADR under discussion), as defined by FDA guidance on criteria for well-documented case report. One case (MWP2007-50068) was identified as meeting the criteria for a well-documented case of shock/anaphylactoid reaction. The search also retrieved 9 cases with PTs of ***Anaphylactic reaction***, **Anaphylactoid reaction**, or **Anaphylactic shock**, including 8 serious cases (MWP2007- 50068, MWP2006-50932, MWP2007-50495, MWP2007-51187, MWP2007-51549, MWP2009-00390, MWP2009-00762, and MWP2010-00403). One case (MWP2007-50471) with the ***PT Shock*** described events consistent with anaphylactic reaction.

I reviewed the above case narratives and concur with the Sponsor that a) using the Sampson criteria (Sampson, Munoz-Furlong et al. 2005) as a guide, they may constitute anaphylaxis and b) a relationship between these cases and the edaravone treatment is possible.

8.6. Integrated Assessment of Safety

Overall, the occurrence of serious safety events (deaths, serious and significant AEs) is low in the RADICAVA ALS program. The postmarketing data from the ALS, acute ischemic stroke, and subarachnoid hemorrhage programs revealed numerous cases that were confounded or were deficient in necessary details to make a decision on causality. The condition of hypersensitivity / anaphylaxis was an exception with 10 potential cases that had a realistic probability of edaravone causality.

The applicant has proposed several categories of Contraindications and Warnings that I have discussed in the Labeling section of this review. The proposal for a contraindication for (b) (4) (b) (4) is both unclear (i.e., does the drug cause (b) (4) or should those with this condition not take the drug?) and not supported. The applicant's own summary of postmarketing safety refutes the evidence potentially supporting this. Because contraindications should not be theoretical or issues that one could not rule out, I suggest not including this in the contraindications section. Similarly, the Warning for (b) (4) (b) (4) is unclear and also not supported for the same reasons described for

The number of patients exposed and duration of exposure are relatively small. I believe standard postmarketing surveillance will be adequate to evaluate if any serious signals will develop. I believe what I have heard from patients / patient representatives is that a drug which demonstrates some clinical benefit could have an acceptable risk/benefit profile; even in the face of moderate levels of safety risk or tolerability issues. Evaluation of the ALS database in conjunction with the relatively large postmarketing dataset suggests that the risks are acceptable at this time and that a favorable risk/benefit profile has been presented for RADICAVA for the intended indication.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was convened to discuss this application. An advisory committee meeting was not deemed necessary to judge whether the data were adequate to establish the efficacy or safety of edaravone for the treatment of amyotrophic lateral sclerosis.

10 Labeling Recommendations

10.1. Prescribing Information

I have the following recommendations for modifying the applicant's proposed labeling:

- **Section 1** is presented with acceptable form and content pending the finalization of the RADICAVA. One might consider whether a limitation of use should be applied because of the apparent lack of effect in patients with more advanced ALS. Since the natural history of ALS may be variable and since there is not clear understanding of when the effectiveness diminishes, I would not recommend this type of labeling.

- **Section 2** is worded in a very complex manner, though it represents what was done in Study 19. A simpler dosing regimen that is generally consistent with that used in Study 19 might be considered.

- **Section 4** I agree with the applicant's contraindication based on hypersensitivity. (b) (4)

- **Section 5**. Several of the proposed Warnings and Precautions e.g., (b) (4), are seemingly because the Sponsor could not discount cases which they have suggested are wither too confounded or incomplete to assign causality.

  I do not agree with inclusion of the general phrases:

  (b) (4)

  The format of Warnings and Precautions should be revised according to the ***Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format.***

- **Section 14** (Clinical Studies) of the FPI is not acceptable in the proposed form. (b) (4) I recommend (b) (4) Study 19 characteristics and key results including, the primary outcome measure, the ALSFRS total score.

10.2. Recommendations on REMS

A REMS is not recommended.

11 Postmarketing Requirements and Commitments

No post-marketing commitments are recommended.

12 Appendices

12.1. References

Oda, E., Y. Ohashi, et al. (1996). "[Reliability and factorial structure of a rating scale for amyotrophic lateral sclerosis]." No To Shinkei **48**(11): 999-1007.

Sampson, H. A., A. Munoz-Furlong, et al. (2005). "Symposium on the definition and management of anaphylaxis: summary report." J Allergy Clin Immunol **115**(3): 584-591.
Wolf, J., A. Safer, et al. (2014). "Factors predicting one-year mortality in amyotrophic lateral sclerosis patients--data from a population-based registry." BMC Neurol **14**: 197.

12.2. Financial Disclosure

None of the Investigators in Study 19 had significant financial disclosures.

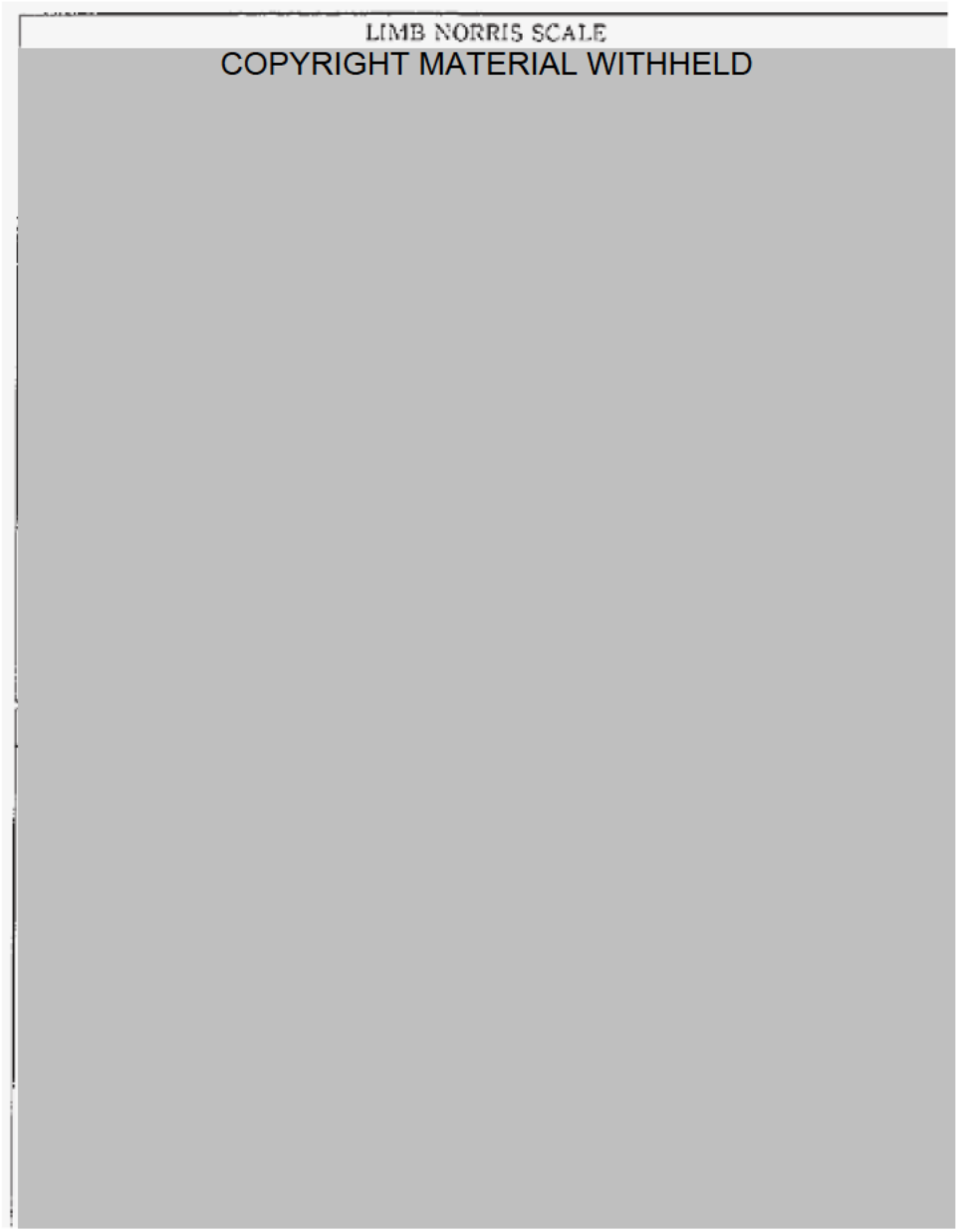
Covered Clinical Study (Name and/or Number): MCI186-19 A Phase III, Double-blind, Parallel-group Study of Edaravone (MCI-186) for Treatment of Amyotrophic Lateral Sclerosis (Second Confirmatory Study)

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 39		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	YesX	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: NA	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) NA		

12.3. Appendices Related to Clinical Review

12.3.1. Appendix 1. Norris Scale

Table 46 Original Modified Norris Scale (left panel) versus the Japanese Translation of the Modified Norris Scale (right panel)



Source (Oda, Ohashi et al. 1996)

12.3.2. Appendix 2 The Japanese ALS Severity Classification

Severity Classification: 1	Able to work or perform housework
2	Independent living but unable to work
3	Requiring assistance for eating, excretion or ambulation
4	Presence of respiratory insufficiency, difficulty in coughing out sputum or dysphagia
5	Using a tracheostomy tube, tube feeding or tracheostomy positive pressure ventilation.

Source: Table 47 protocol250/267

12.3.3. Appendix 3. Study Sites – Study 19

Table of Demographic Characteristics

Site Name	ID	# Pts	Site Name	ID	# Pts
Jichi Medical University Hospital	04	10	National Hospital Organization Miyagi National Hospital	03	4
Kansai Medical University Hirakata Hospital	21	4	National Hospital Organization Nagasaki Kawatana Medical Center	22	4
Kitasato University East Hospital	09	7	National Hospital Organization Nishi-Niigata Chuo National Hospital	25	5
Mie University Hospital	20	2	National Hospital Organization Shizuoka Institute of Epilepsy and Neurological Disorders	11	6

Site Name	ID	# Pts	Site Name	ID	# Pts
Murakami KARINDOH Hospital	17	6	National Hospital Organization Toneyama National Hospital	15	6
Nagoya University Hospital	12	8	National Hospital Organization Utano Hospital	23	5
National Hospital Organization Chiba-East-Hospital	24	4	Nippon Medical School Hospital	07	2
National Hospital Organization Higashi Nagoya National Hospital	13	4	Okayama University Hospital	16	12
National Hospital Organization Higashisaitama Hospital	05	4	Osaka Prefectural Hospital Organization Osaka General Medical Center	14	7
National Hospital Organization Hokkaido Medical Center	01	4	Saitama Neuropsychiatric Institute	06	6
National Hospital Organization Iou Hospital	26	6	Seirei Social Welfare Community Seirei Hamamatsu General Hospital	10	1
National Hospital Organization Kumamoto Saishunso National Hospital	18	8	The University of Tokyo Hospital	08	7
			Toho University Omori Medical Center	28	3

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/s/

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05/02/2017

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05/02/2017