CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209176Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	209176
Link to EDR	\\CDSESUB1\evsprod\NDA209176\209176.enx
Submission Date	6/16/2016
Submission Type	Standard Review (expedited)
Brand Name	RADICAVA
Generic Name	Edaravone
Dosage Form and Strength	Solution (30 mg /100 mL)
Route of Administration	Intravenous infusion
Proposed Indication	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Applicant	Mitsubishi Tanabe Pharma Corporation
Associated IND	126396
OCP Review Team	Xinning Yang, Ph.D., Atul Bhattaram, Ph.D. Kevin Krudys, Ph.D., Sabarinath Sreedharan, Ph.D.
OCP Final Signatory	Mehul Mehta, Ph.D.

The Review Team acknowledges the input from OCP Guidance and Policy Team to this review.

Table of Contents

1. EXECUTIVE SUMMARY

The applicant is seeking approval for edaravone, a free radical scavenger, to treat amyotrophic lateral sclerosis (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. Currently, riluzole is the only drug approved for ALS.

The proposed dosing regimen for edaravone includes an initiation regimen followed by a maintenance regimen. Treatment initiation is with 60 mg edaravone administered intravenously (IV) over 60 minutes daily for 14 consecutive days followed by a 2-week drug free period. This initiation regimen is followed by administration of 60 mg IV over 60 minutes daily for 10 days within a 14 day period followed by a 2-week drug free period (maintenance regimen). This is the same dosing regimen tested in Phase 3 trials.

The efficacy and safety of edaravone is supported by four Phase 3 trials conducted in Japanese patients with ALS with different degrees of disease severity. The applicant followed an enrichment strategy using information from earlier studies to identify a relatively homogenous subpopulation of ALS patients in whom edaravone showed beneficial treatment effects (see Appendix 4.5 for details). Subsequently, efficacy was demonstrated with statistical significance in a pivotal study (MCI186-19) in this prospectively selected subpopulation of ALS patients[1]. The safety and efficacy findings from these studies are considered applicable to all ALS patients (see Clinical Review by Dr. Christopher Breder for details).

The efficacy/safety studies of edaravone were conducted in Japan and did not include US population. Therefore, the applicant relied on population pharmacokinetic (PK) analysis using clinical pharmacology studies conducted in Japanese and European Caucasian healthy subjects to demonstrate PK similarity between these two races. No exposure data were collected from ALS patients during the clinical development program and no exposure-response analyses were performed. Considering the similarity between the US and Japanese populations for edaravone PK (see Section 3.3.1 for details), similar disease identification/progression of ALS and clinical practice/treatment guidelines for ALS between US and Japan (see Clinical Review by Dr. Christopher Breder), the proposed dosing regimen and efficacy/safety results of edaravone are considered acceptable.

1.1 Recommendations

We recommend approval of NDA 209176 from a Clinical Pharmacology perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence came from a Phase 3 study (MCI186-19) conducted in Japanese patients with ALS. Three additional Phase 3 studies in ALS patients provided additional safety information. The applicant performed population PK analyses to demonstrate PK

[1] Change in Revised ALS Functional Rating Score (ALSFRS-R) from baseline was used as the primary efficacy endpoint.

	similarity between Japanese and Caucasian population for edaravone. The ALS disease progression and treatment guidelines/clinical practices are also considered similar between Japan and the US (refer to Clinical Review for additional details).
General dosing instructions	The proposed dosing regimen is the same as that tested in Phase 3 trials and includes an initiation regimen followed by a maintenance regimen. Initiation regimen: 60 mg edaravone administered IV over 60 minutes daily for 14 consecutive days followed by a 2-week drug free period. Maintenance regimen: 60 mg edaravone IV over 60 minutes daily for 10 days within a 14 day period followed by a 2-week drug free period.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose individualization is recommended based on intrinsic and extrinsic factors. Edaravone is extensively metabolized and excreted mainly as glucuronide and sulfate conjugates. It is possible that edaravone exposure may be increased in patients with hepatic impairment. However, considering the severity of ALS, very limited treatment options for ALS, general safety profile of edaravone, its unique dosing regimen (on and off), clinical experience with certain higher exposure of edaravone in previous PK studies, we deemed that the proposed dosing regimen can be used in patients with mild and moderate hepatic impairment with careful monitoring for its adverse events. However, severe hepatic impairment in ALS presents a complex clinical scenario. No dosing recommendations can be provided in severe hepatic impairment until a study is performed to assess edaravone PK in that population.
Labeling	The proposed label is generally acceptable. However, the review team has some specific recommendations for content and format.
Bridge between the to-be-marketed and clinical trial formulations	A solution formulation in ampoule (30 mg /20 mL) was used in Phase 3 trials, and was diluted to 140 mL with saline for IV administration. The to-be-marketed product will be provided in a bag instead of ampoules and will be administered as 200 mL solution in saline. The difference of 60 mL volume in infusion solution is not considered clinically relevant.

1.2 Post-Marketing Requirements and Commitments

We recommend a PMR study to evaluate the PK of edaravone in patients with severe hepatic impairment.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Edaravone is a free radical-scavenger. Reducing oxidative stress is a postulated mechanism of action of edaravone for the treatment of ALS.

Edaravone is metabolized into pharmacologically inactive sulfate and glucuronide conjugates. The maximum plasma concentration of edaravone was reached by the end of infusion and there was no accumulation in plasma concentration after multiple dosing. The terminal half-life of edaravone was about 4.5 - 6 hours. There was a trend of more than dose proportional increase in AUC and C_{max} of edaravone with increasing doses. Edaravone and its metabolites are excreted into urine, accounting for 70-80% or more of the administered dose with very little as unchanged drug (about 1% or less).

Population PK analyses suggested that gender, age, or weight did not affect the PK of edaravone. Race had only a modest effect on the peripheral volume of distribution of edaravone. The PK data of edaravone in patients with renal impairment or hepatic impairment are not currently available.

Based on results from *in vitro* experiments, at the therapeutic dose, edaravone and its metabolites are not anticipated to inhibit major CYP enzymes or transporters. Edaravone or its metabolites are not expected to induce CYP1A2, 2B6, or 3A4/5 in humans, either. Since edaravone is metabolized by multiple Phase II enzymes (uridine diphosphate glucuronosyltransferase (UGT) isozymes, and sulfotransferase) and has a high passive permeability, its PK is less subject to the impact of inhibitors or inducers of CYP enzymes, UGTs, or transporters. Overall, the drug-drug interaction (DDI) potential for edaravone is considered low.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen of edaravone is the same as that tested in the Phase 3 trials and is acceptable. The treatment initiation is with 60 mg edaravone administered IV over 60 minutes daily for 14 consecutive days followed by a 2-week drug free period (initiation regimen). This initiation regimen is followed by administration of 60 mg IV over 60 minutes daily for 10 days within a 14 day period followed by a 2-week drug free period (maintenance regimen).

2.2.2 Therapeutic individualization

No individualized dosing is required. Gender, age, weight, or race did not have significant effect on the clearance and AUC of edaravone. Thus, there is no evidence to support the need for individualized dosing regimen based on these intrinsic factors.

PK data of edaravone in patients with hepatic impairment are not available. Edaravone is mainly metabolized in the liver and cleared as a sulfate and a glucuronide conjugates in the urine. We considered the following for not recommending any dose adjustments in mild and moderate hepatic impairment:

1) Mild and moderate hepatic impairment in general have relatively limited impact on the exposure of drugs cleared mainly as conjugates. This may be due to the presence of extra-hepatic Phase II enzymes available in the body.

2) Edaravone has a short elimination $t_{1/2}$ (4.5-6 hrs) and does not accumulate after repeated doses. Also the proposed maintenance dosing regimen includes drug treatment for 10 days followed by a two week drug-free period. This may effectively work as a washout period.
3) The safety profile of edaravone is considered fairly benign (Please also refer to section 3.3.3 for possible safety margin from previous clinical PK studies).
4) ALS is a devastating disease with very limited treatment options.

In patients with severe hepatic impairment, the increase in systemic exposure (e.g., C_{max}) to edaravone could be significantly greater than the current clinical experience and the potential impact cannot be fully assessed without PK data/clinical experience in such patients. Thus, we recommend a PMR study to evaluate the impact of severe hepatic impairment on the PK of edaravone. Also, the label should state that a dosing recommendation cannot be provided in patients with severe hepatic impairment. This labeling statement will be updated once the PMR study report is available.

2.3 Outstanding Issues

(b) (4)

Nevertheless, a renal impairment study is not necessary and no dosing adjustment is needed in patients with renal impairment, due to the following reasons:

1) Negligible elimination of edaravone into urine as parent drug (1 % or less)
2) The glucuronide and sulfate conjugate metabolites are inactive. Per the pharmacology /toxicology reviewer, there is no significant concern about the toxicity of these metabolites.
3) Some of the justifications listed in Section 2.2.2 for hepatic impairment are also applicable here.
4) Lastly, the incidence of treatment emergent adverse events (TEAEs) in the mild renal impairment group compared to the normal renal function group were similar in the ALS patients in the Phase 3 trials (see Section 3.3.3 for details).

2.4 Summary of Labeling Recommendations

We recommend that edaravone can be given to ALS patients regardless of their renal function. No dose adjustment is needed for patients with mild or moderate hepatic impairment, either. No specific dosing recommendation can be provided for severe hepatic impairment. This recommendation will be updated when the data from the PMR study become available (see Sections 2.2.2 and 3.3.3 for more details).

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Currently, riluzole is the only drug approved for the treatment of ALS in U.S. Edaravone is developed as a solution for IV infusion use. It was first approved in 2001 in Japan for the treatment of acute ischemic

stroke as IV infusion of 30 mg edaravone administered over 30 minutes, twice a day for up to 14 days. Edaravone was also approved in Japan and in South Korea in 2015 for the treatment of ALS.

On May 12, 2015, edaravone received orphan designation from the Agency for the treatment of ALS. On June 16, 2015, the applicant met with the Division in a Pre-IND meeting (IND 126396) to discuss the efficacy findings of a Phase 3 study of edaravone for the treatment of ALS and to obtain agreement as to the regulatory pathway needed for approval. This was followed by a Pre-NDA meeting held on December 9, 2015.

The to-be-marketed product of edaravone is a solution formulation for IV infusion.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Edaravone is a free radical-scavenger. Alleviation of oxidative stress by removing free radical is a postulated mechanism of action.
Active Moieties	Edaravone is the active moiety. Metabolites of edaravone are considered pharmacologically inactive.
QT Prolongation	The applicant has not conducted a TQT study. Please refer to Clinical review and QT-IRT review for additional details.
General Information	
Bioanalysis	Edaravone and its metabolites in plasma and urine were measured using validated GC/MS or LC-MS/MS methods. A summary of the method validation specifications is included in Appendix 4.1.
Healthy Volunteers vs. Patients	No PK data were obtained from ALS patients. The PK of edaravone in ALS patients is not expected to be different from that in healthy subjects. Edaravone is eliminated through sulfate and glucuronide conjugation. There was no evidence suggesting that these metabolic pathways are different between ALS patients and healthy subjects.
Dose Proportionality	There was a trend of more than dose proportional increase in AUC and C_{max} of edaravone (from a single dose of 0.2 mg/kg to 1.5 mg/kg).
Accumulation	No accumulation of edaravone after once daily or twice daily dosing.
Variability	Variability (%CV) of C_{max} and AUC of edaravone was about 20% or less.
Absorption	
Bioavailability	Edaravone is given intravenously.
T_{max}	At the end of infusion.

Distribution	
Volume of Distribution	Around 70 L (Vss) based on population PK analysis.
Plasma Protein Binding	91-92%. Mainly due to binding with albumin.
Blood to Plasma Ratio	Not available.
Substrate transporter systems	It is a weak substrate of OAT1 and OAT3.
Elimination	
Mean Terminal Elimination half-life	About 4.5 - 6 hours for edaravone, and 2 – 2.8 hours for its metabolites.
Metabolism	
Primary metabolic pathway(s) [*in vitro*]	Edaravone is metabolized into a sulfate conjugate and a glucuronide conjugate. The glucuronidation is mediated by multiple UGT isozymes, while the sulfate conjugate is presumed to be formed by sulfotransferases.
Inhibitor/Inducer	Edaravone inhibited CYP2C9, BCRP, OAT3, and induced CYP1A2 *in vitro*. Edaravone sulfate conjugate inhibited OAT1 and OAT3 *in vitro*. The *in vivo* DDI potential is considered low at the proposed dose level. Please refer to Appendix 4.4 for details.
Excretion	
Primary excretion pathways	Edaravone and its metabolites were excreted into urine, accounting for 70-80% or more of the administered dose, with glucuronide conjugate as the predominant moiety. Less than 1% of the dose was excreted as parent drug.
Intrinsic Factors	
Demographics	Gender, age, or weight did not affect PK of edaravone. Race has an effect only on the peripheral volume of distribution of edaravone (i.e., a 26% difference for peripheral volume of distribution between Caucasian and Japanese).
Diseases	PK data of edaravone in patients with renal impairment or hepatic impairment are not available. Per the applicant, they have started preparations and will perform studies in patients with mild and moderate renal/hepatic impairment in Japan. The data will be submitted upon completion expected in late 2017 to early 2018.

3.3 Clinical Pharmacology Review Questions

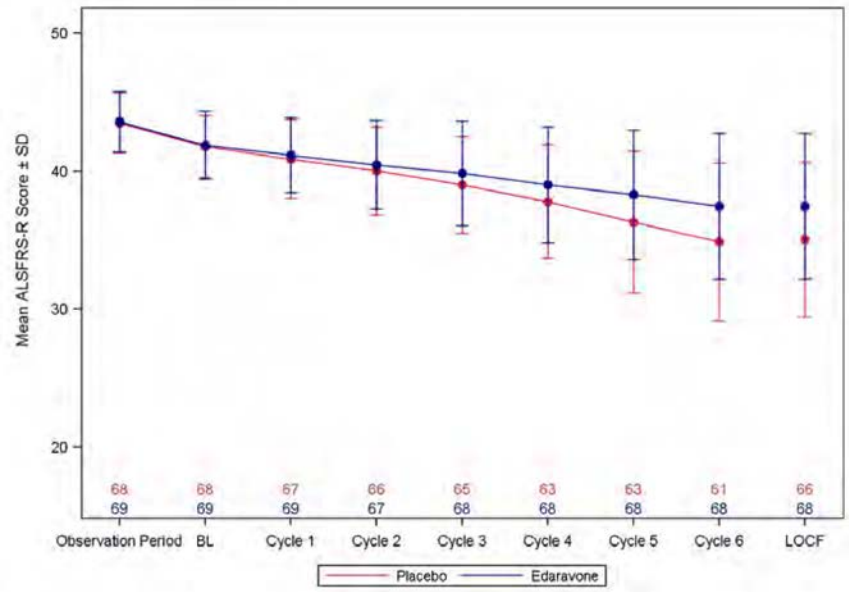
3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The pivotal evidence for effectiveness comes from a 24-week, randomized, placebo-controlled, double-blind, parallel-group study (MCI186-19). Edaravone was administered as 60 mg/day in Japanese patients with ALS severity grades 1 and 2 based on Japan ALS severity classification. The study population was enriched by inclusion criteria, defined as the Definite or Probable/ Efficacy Expected Subpopulation /2 year population. This is a subpopulation of ALS patients who had functionality retained in most activities of daily living (ADL) domains with normal respiratory function, named as Efficacy Expected Subpopulation (EESP). In addition to the EESP criteria, subjects had to meet the following two criteria to be defined as 'Definite or Probable/EESP/2y' population.

- Definite or Probable ALS diagnosis based on the El Escorial and revised Airlie House diagnostic criteria at preregistration (to ensure diagnosis of ALS)
- Within 2 years of initial ALS symptom onset at pre-registration (to exclude subjects who were stable for long term with ALS).

Edaravone demonstrated a statistically significant difference of 2.49 units (95% CI: 0.99, 3.98) in the primary endpoint, revised ALS functional rating scale (ALSFRS-R score), compared to placebo (Figure 1).

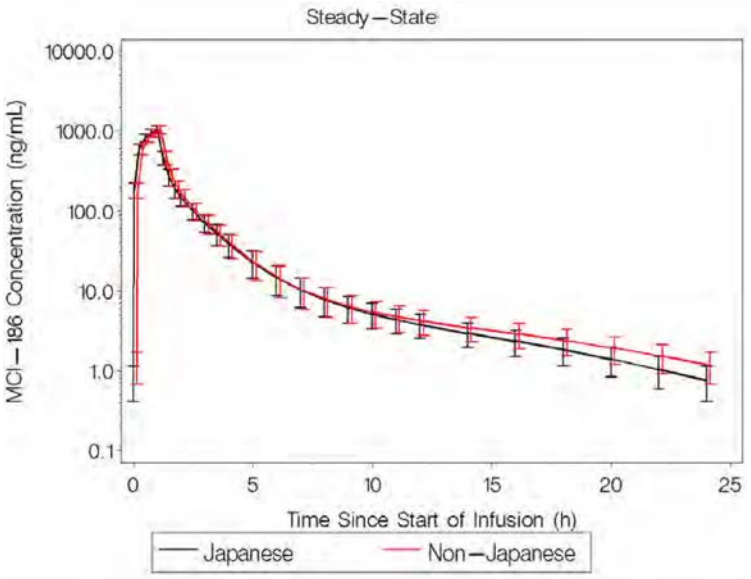
Figure 1. ALSFRS-R Score (Mean ± SD) Over Time (Study MCI186-19 Double-blind Phase, Full Analysis Set, Observed Cases)



(Source: Clinical Overview, page 31)

There is no direct evidence of effectiveness of edaravone in the US population, as all the efficacy trials for ALS were conducted in the Japanese population. However, population PK analysis provided evidence that the PK of edaravone is similar between the US (Caucasians) population and Japanese population. The applicant performed population PK analyses utilizing PK data from all the five Phase 1 studies conducted in healthy subjects (3 in Japan, 2 in EU). Simulations using the PK model demonstrated that there is no difference in AUC and C_{max} of edaravone between Japanese and Caucasian healthy subjects with the proposed dosing regimen (Figure 2, See Appendix 4.3 for more details).

Figure 2. Mean (± Standard Deviation) Plot of Simulated Edaravone Concentration versus Time Since Start of Infusion in Virtual ALS Patients for a Dose of 60 mg Infused over 1 Hour (Displayed on a Log-Linear Scale)



(Summary of Clinical Pharmacology, page 64)

PK data in patients with ALS have not been obtained. The PK of edaravone in ALS patients is not expected to be different from that in healthy subjects, since edaravone is eliminated through sulfate and glucuronide conjugation. There was no evidence suggesting that these metabolic pathways are different between ALS patients and healthy subjects.

Since the population PK dataset only contains PK data from Japanese and Caucasian populations, it does not provide direct evidence for the comparison between African American or Hispanic populations to the Japanese population. However, it is not expected that the PK of edaravone will be significantly different in these populations. There is no report of specific polymorphism of sulfotransferase indicating potential differences among races/ethnic groups. UGT1A9 appeared to be the main contributor of glucuronidation of edaravone. While there is a report suggesting potential gene variant of UGT1A9, the impact of the ethnic/race differences on the PK of edaravone is unlikely to be clinically relevant as edaravone is metabolized with multiple UGTs, and sulfate conjugation is the major metabolic pathway of edaravone. Thus, it is concluded that the PK of edaravone is similar between the US and Japanese patients with ALS.

Besides PK similarity, the applicant also stated that the clinical practice and treatment guidelines for ALS between Japan and North America are very similar, and no important differences were noted in ALS disease identification and progression. Also, per the applicant, there were no new safety findings in European studies in healthy volunteers and stroke patients who received edaravone. Please refer the review of Medical Officer, Dr. Christopher Breder, for more details.

Taken together, these pieces of evidence support the effectiveness of edaravone in US patients with ALS.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The PK data analyses demonstrated that the dosing regimen shown to be effective in the Phase 3 trials will result in similar plasma concentrations of edaravone in US patients with ALS as compared to Japanese patients. Thus, from a PK perspective, the dosing regimen investigated in the Phase 3 trials is appropriate for the US patients with ALS.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Gender, age, weight, or race did not have significant effect on the PK of edaravone.

Hepatic Impairment:

PK data of edaravone in patients with hepatic impairment are not available. However, there is no evidence to suggest that the dosing regimen needs to be adjusted for patients with mild or moderate hepatic impairment. A PMR study is recommended to characterize the impact of severe hepatic impairment on the PK of edaravone. In addition to the rationale described in Section 2.2.2, there may also be some safety margin from previous PK studies, though it is acknowledged that these studies were conducted in small groups of healthy subjects. The C_{max} and $AUC_{0\text{-}24hr}$ of edaravone in the US population under the proposed dosing regimen are estimated to be about 1049 ng/mL and 1374ng*hr/mL, respectively (see Table 20 in Appendix 4.3). In a previous PK study (MCI186-01), one cohort of healthy subjects (n = 5) received edaravone 1 mg/kg once daily (infused over 40 min) for 7 days and had C_{max} around 1700 – 1800 ng/mL. In another study (MCI86-E02), one cohort of healthy elderly subjects (n = 10) received edaravone bolus dose of 0.2 mg/kg followed by an infusion for 24 hrs at a rate of 0.5 mg/kg/hr. The mean AUC of edaravone in this cohort was about 24136 ng*hr/mL. The concentration of edaravone was maintained at a level around 1000 ng/mL for 24 hrs, while the edaravone concentration at the proposed dosing regimen rapidly decreases after the end of infusion (i.e. from 1 hr post initiation of infusion, Figure 2). The adverse events in Studies MCI186-01 and MCI186-E02 were considered mild to moderate in intensity. Though these dosing regimens are not the same as the proposed dosing regimen for ALS patients, the results may still provide certain safety margins for the potential increase in edaravone concentrations in patients with mild or moderate hepatic impairment. It is noteworthy that edaravone has a short elimination $t_{1/2}$ (4.5-6 hrs) and does not accumulate after repeated doses. Also the proposed maintenance dosing regimen includes drug treatment for 10 days followed by a two week drug-free period. This may effectively work as a washout period.

Renal Impairment:

No PK data are currently available from subjects with any degree of renal impairment. However, based on the metabolic pathways of edaravone and the minimal renal elimination of edaravone as unchanged drug (1% or less), edaravone plasma concentrations are less likely to increase significantly in patients with renal impairment. We acknowledge that the exposure of some non-renally eliminated drugs increased significantly in patients with severe renal impairment. However, this seemed to happen mainly for drugs that are metabolized by CYP enzymes (especially CYP2D6)[2]. The metabolism of edaravone does not involve CYPs.

In addition, the applicant summarized the adverse events in subjects with different degrees of renal function (classified using CLcr) who participated in the Phase 3 trials for ALS. Among subjects that had

[2] Yoshida K, et al. Clin Pharmacol Ther. 2016 Jul;100 (1):75-87.

moderate renal impairment (N=6), 4 out of 4 subjects in the placebo group and 2 out 2 subjects in the edaravone group experienced a TEAE. Since the number of subjects with moderate renal impairment in the Phase 3 studies is very small, no comparisons or definitive conclusions can be made regarding the TEAEs observed in this renal function group.

According to the applicant, among subjects that had mild renal impairment (N=93), 83.3% (35/42) in the placebo group and 84.3% (43/51) in the edaravone group experienced a TEAE. Among subjects with normal renal function (N=269), 87.7% (121/138) in the placebo group and 88.5% (116/131) in the edaravone group experienced a TEAE. The overall incidence of TEAEs is similar between placebo and edaravone for the mild renal function group. In addition, there is no imbalance observed in overall incidence of TEAEs in the mild renal impairment group compared to the normal renal function group.

Thus, the safety information obtained from Phase 3 trials for ALS suggested that mild impairment in renal function does not have a significant impact on the safety profile of edaravone for the proposed dosing regimen.

Overall, we conclude that there is no need for dosing adjustment in patients with renal impairment.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. Edaravone is administered via IV route. The drug-interaction potential involving edaravone is considered low. Edaravone and its metabolites are not anticipated to inhibit major CYP enzymes or transporters *in vivo*. Edaravone and its metabolites are not expected to induce CYP1A2, 2B6, or 3A4/5 in humans, either. Since edaravone is metabolized by multiple Phase 2 enzymes (UGTs and sulfotransferases) and has a high passive permeability, its PK is less subject to the impact of inhibitors or inducers of CYP enzymes, UGTs, or transporters. Please refer to Appendix 4.4 for details.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

A gas chromatography-mass spectrometry (GC-MS) method was initially developed and used for Studies MCI186-01, MCI186-10, and MCI186-E01. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was subsequently developed in order to simplify pretreatment of samples and improve operational efficiency. The LC-MS/MS method was used in Studies MCI186-14 and MCI186-E02. These assays were validated individually.

Table 1. Summary of Bioanalytical Methods in Each Clinical PK Study – Plasma

Study	Facility	Analytical method	Analyte	Sample volume (mL)	Analytical range (ng/mL)	Variables		Stability (condition/period)
						Precision (CV, %)	Accuracy (RE, %)	
MCI186-01	(b) (4)	GC-MS	Edaravone	0.5	0.1-1000	1.5-5.0	NC	See 521120
MCI186-10		GC-MS	Edaravone	0.5	1-5000	2.4-10.4	-7.1-5.5	-20°C / 4 months[c]
			Glucuronide[a]	0.5	1-5000	0.3-11.1	-10.0-4.7	-20°C / 4 months[c]
			Sulfate[b]	0.5	1-5000	0.8-10.4	-15.0-5.9	-20°C / 4 months[c]
MCI186-E01		GC-MS	Edaravone	0.5	5-500	0.8-14.2	-2.6-4.4	-70°C / 25 months[d]
MCI186-14		LC-MS/MS	Edaravone	0.5	2-5000	1.4-10.5	-6.3-8.2	See 521120
			Glucuronide[a]	0.5	5-5000	1.3-6.2	-6.6-7.2	See 521120
			Sulfate[b]	0.5	2-5000	2.0-6.0	0.3-13.3	See 521120
MCI186-E02 and E04		LC-MS/MS	Edaravone	0.5	2-5000	1.5-4.5	-15-0.5	-70°C / 9 months[d]
			Glucuronide[a]	0.5	2-5000	1.5-4.5[e]	-15-0.5[e]	-70°C / 12 months[d]
			Sulfate[b]	0.5	2-5000	1.5-4.5[e]	-15-0.5[e]	-70°C / 12 months[d]

NC = not calculated, RE% = percent relative error (accuracy).
[a] Glucuronide conjugate of edaravone.
[b] Sulfate conjugate of edaravone.
[c] In solvent.
[d] In plasma with stabilizer.
[e] Data of edaravone was applied. Glucuronide and sulfate conjugates of edaravone were hydrolyzed through heat-acid or acid treatments to edaravone, respectively, and then the edaravone concentrations obtained were calculated to the concentration of the conjugates.
(Source: Summary of biopharmaceutic studies and associated analytical methods, page 10)

Table 2. Summary of Bioanalytical Methods in Each Clinical PK Study – Urine

Study	Facility	Analytical method	Analyte	Sample volume (mL)	Analytical range (ng/mL)	Variables		Stability (condition/period)
						Precision (CV, %)	Accuracy (RE, %)	
MCI186-01	(b) (4)	GC-MS	Edaravone	1	50-2000	0.8-2.3	NC	-20°C / 31 days[d]
			Glucuronide[a]	1	50-2000[e]	0.8-2.3[e]	NC	-80°C / 13 days
			Sulfate[b]	1	50-2000[e]	0.8-2.3[e]	NC	-80°C / 13 days
MCI186-10		GC-MS	Edaravone	1	50-2000	0.9-4.5	-2.3-3.1	See PRD02-138
			Glucuronide[a]	1	50-2000[e]	0.9-4.5[e]	-2.3-3.1[e]	See 951570
			Sulfate[b]	1	50-2000[e]	0.9-4.5[e]	-2.3-3.1[e]	See 951570
MCI186-E01		GC-MS	Edaravone	1	50-25000	0.6-7.9	0.4-9.8	-70°C / 2 years[d]
MCI186-14		LC-MS/MS	Edaravone	0.05	20-50000	1.6-11.3	-2.2-10.4	-20°C / 1 year[c]
			Glucuronide[a]	0.05	20-50000	0.7-8.7	-4.0--0.1	-20°C / 1 year[c, f]
			Sulfate[b]	0.05	20-50000	0.5-9.8	-1.0-4.1	-20°C / 1 year[c, f]
MCI186-E02		LC-MS/MS	Edaravone	0.05	20-50000	1.5-6.3	-15.0--1.3	See PRD02-138
			Glucuronide[a]	0.05	20-50000	1.5-6.3[e]	-15.0--1.3[e]	See PRD02-138
			Sulfate[b]	0.05	20-50000	1.5-6.3[e]	-15.0--1.3[e]	See PRD02-138

The footnotes are the same as Table 1 except the following,
[d] In urine with stabilizer.
[f] Data of edaravone was applied. Glucuronide and sulfate conjugates of edaravone were hydrolyzed through heat-acid or acid treatments to edaravone, respectively, and then the edaravone concentrations obtained were

calculated to the concentration of the conjugates. Samples for glucuronide and sulfate conjugates of edaravone were stored after heat-acid or acid treatments, respectively.
(Source: Summary of biopharmaceutic studies and associated analytical methods, page 11)

The applicant has not performed cross-validation between the two methods. To evaluate the potential impact of bioassays on PK measurements, we conducted cross-study comparisons on the PK results obtained from the GC-MS method vs. LC-MS/MS method. It should be noted that the dosing regimens varied among the five PK studies (Table 3) and there is nonlinear PK of edaravone which is dependent on the doses of edaravone. It appears that the dosing regimens in studies MCI186-E01 and MCI186-E02 are relatively close, while the dosing regimens of studies MCI186-01 and MCI186-02 deviate significantly from that in study MCI186-14.

In study MCI186-E01, edaravone was administered as 1.8 mg/kg infused over 6 hrs, i.e., an infusion rate of 0.3 mg/kg/hr. This is close to the infusion rate of the dosing group of a bolus dose of 0.1 mg/kg plus 0.25 mg/kg/hr long-term infusion (almost 24 hrs) in study MCI186-E02. In addition, both subjects participating in these two studies were healthy elderly European subjects.

Table 3. Dosing Regimens and Sampling Plans of PK studies

Study Number	Design	Treatment	Dosage	Planned Number of Postdose PK Samples Per Subject
MCI-186-J01	SB, PC, HV	Single dose	40-minute iv infusion at 0.2, 0.5, 1.0, 1.5 mg/kg and 3-hour iv infusion at 2.0 mg/kg	15
		Multiple dose 7 days/ doses	40-minute iv infusion at 1.0 mg/kg daily for 7 days	39
MCI-186-J10	SB, PC, HV	Multiple dose 2 days/ 4 doses	30-minute iv infusion at 0 and 0.5 mg/kg twice daily for 2 days	14
MCI-186-J14	OL, HV	Single dose	48-hour iv infusion at 120 mg/day	22
MCI-186-E01	DB, PC, HV	Single dose	6-hour iv infusion at 0.6 and 1.8 mg/kg	19
MCI-186-E02	DB, PC, HV	Bolus + continuous infusion	0.05 mg/kg (3 minutes) + 0.125 mg/kg/h for 23.95 hours 0.1 mg/kg (3 minutes) + 0.25 mg/kg/h for 23.95 hours 0.2 mg/kg (3 minutes) + 0.5 mg/kg/h for 23.95 hours	20

Abbreviations: DB, double blind; HV, healthy volunteer; iv, intravenous; OL, open label; PC, placebo controlled; PK, pharmacokinetic; SB, single blind.

(Source: Population PK analysis study report, page 54)

The CL of edaravone (at 1.8 mg/kg dose) from study MCI186-E01 was 12.3 mL/kg/min (Table 4). After multiplied by body weight (mean value 71.3 kg), the CL was 52619.4 mL/hr. The CL of edaravone for the 0.1 mg/kg bolus and 0.25 mg/kg/hr dose group of study MCI186-E02 E02 was 46994.4 mL/hr (Table 5). So, the CL of edaravone from study MCI186-E01 (measured with GC-MS method) was just 12% higher than that from study MCI186-E02 (measured with LC-MS/MS method), which is considered a minor difference.

Table 4. Summary of PK Parameters of Edaravone in Study MCI186-E01

Analyte	MCI-186	
Parameter	A: 0.6 mg/kg MCI-186 (n = 10)	B: 1.8 mg/kg MCI-186 (n = 10)
AUC(0-t_z) [h*ng/mL]	448 (%CV: 19.3)	2397 (%CV: 20.0)
AUC(0-48) [h*ng/mL]	455 (%CV: 18.9)	2418 (%CV: 20.0)
AUC(0-∞) [h*ng/mL]	463 (%CV: 18.9)	2447 (%CV: 20.8) *
C_{max} [ng/mL]	91 (%CV: 20.5)	477 (%CV: 20.5)
C_{6h} [ng/mL]	91 (%CV: 20.5)	473 (%CV: 21.1)
t_{max} [h]	6 (range: 6-6)	6 (range: 4-6)
CL [mL/kg/min]	21.6 (%CV: 18.9)	12.3 (%CV: 20.8) *
V_z [L/kg]	2.77 (%CV: 15.9)	3.75 (%CV: 42.9) *
t½ [h]	1.48 (%CV: 22.7)	3.53 (%CV: 33.9) *
Ae [μg]	176 (SD: 133.1)	1045 (SD: 885.9)
Ae% [%]	0.40 (SD: 0.26)	0.79 (SD: 0.68)
CL_R [mL/min]	5.04 (%CV: 88.0)	5.43 (%CV: 82.7)

* This parameter could be estimated with sufficient reliability only for 9 cases.

(Source: Study report of MCI186-E01, page 55)

Table 5. Individual plasma PK parameters of the unchanged form of edaravone. Group 1-PK population: 0.1 mg/kg+0.25 mg/kg/h Edaravone in Study MCI186-E02.

Subject	C_{max}	C_{end}	C_{ave}	C_{7min}	T_{max}	K_{el}	$T_{1/2}$	AUC_{0-inf}	AUC_{0-last}	AUC_{0-24h}	AUC_{24-48h}	AUC_{0-48h}	CL	CL	Vz
	(ng/mL)	(ng/mL)	(ng/mL)	(ng/mL)	(hr)	(1/hr)	(hr)	(hr*ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(hr*ng/mL)	(mL/hr)	((mL/hr)/kg)	(L/kg)
2	631	624	575	436	12.00	0.10	6.71	15884	15642	12652	2990	15642	29104	387	3.75
3	625	625	464	468	24.00	0.10	7.16	11191	11147	10441	706	11147	35736	567	5.86
4	522	522	370	449	24.00	0.09	7.31	9109	9070	8450	620	9070	51991	670	7.07
5	464	440	380	464	0.12	0.10	6.93	9165	9131	8616	516	9131	50118	669	6.68
7	428	428	392	385	24.00	0.08	8.17	9649	9603	9024	579	9603	51203	602	7.09
9	475	450	447	469	1.00	0.09	7.37	10956	10909	10163	746	10909	46428	557	5.93
12	435	435	376	408	24.00	0.12	5.67	9364	9341	8695	645	9341	43522	634	5.19
13	464	464	369	411	24.00	0.11	6.37	8792	8769	8237	532	8769	53727	701	6.44
14	389	311	286	389	0.12	0.09	7.31	7123	7102	6752	350	7102	54948	861	9.08
108	369	355	326	302	2.00	0.10	6.64	8226	8200	7668	532	8200	53166	745	7.14
N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	480.0	465.4	398.4	418.0	13.524	0.100	6.965	9945.9	9891.4	9069.8	821.6	9891.4	46994.4	639.4	6.424
St dev	89.1	101.8	80.4	51.6	11.547	0.010	0.675	2399.7	2338.5	1655.5	769.9	2338.5	8552.4	126.0	1.405
Median	464.0	445.3	378.2	423.5	18.000	0.098	7.045	9264.4	9236.0	8655.5	599.6	9236.0	50660.2	651.6	6.563
Minimum	369	311	286	302	0.12	0.08	5.67	7123	7102	6752	350	7102	29104	387	3.75
Maximum	631	625	575	469	24.00	0.12	8.17	15884	15642	12652	2990	15642	54948	861	9.08
CV	18.6	21.9	20.2	12.3	85.4	10.1	9.7	24.1	23.6	18.3	93.7	23.6	18.2	19.7	21.9
Geomean	472.9	455.4	391.6	414.8	-	0.100	6.935	9725.1	9679.0	8942.6	671.4	9679.0	46169.5	627.1	6.275
GeoCV	0.3	0.3	0.3	0.3	-	1104.5	15.9	0.0	0.0	0.0	0.3	0.0	0.0	0.2	20.2
95% CI[22]	416.1-537.5	389.2-533.0	341.1-449.5	376.9-456.5	-	0.093-0.107	6.462-7.443	8334.1-11348.4	8313.7-11268.5	7890.5-10135.0	448.1-1006.1	8313.7-11268.5	39806.1-53550.2	538.4-730.5	5.304-7.424

(Source: Study report of MCI186-E02, page 77)

In addition, a cross-study comparison for the 0.5 mg/kg dose group between studies MCI186-01 (infused over 40 min) and the young adult cohort of MCI186-10 (infused over 30 min) suggested that the CL of edaravone in study MCI186-01 was 27.7% higher than that from study MCI186-10 (back-calculated from AUC of edaravone, Tables 6 and 7). The PK results from both studies were determined by the GC-MS method. This difference is even higher than the difference of edaravone CL observed between studies MCI186-E01 vs MCI186-E02, for which the PK results were determined by different methods (GC-MS vs. LC-MS/MS).

Table 6. PK parameters obtained from plasma unchanged edaravone concentrations for 12 hours after first administration in Study MCI186-10.

	Subject ID	C_{max} (ng/mL)	C_{min} (ng/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2\alpha}$ (hr)	$t_{1/2\beta}$ (hr)	CL_{tot} (mL/hr/kg)	V_{dss} (L/kg)	Ccr* (mL/min)
Healthy elderly subjects	a	900.1	1.4	670	0.19	2.04	746.3	0.87	96.5
	c	1005.1	2.9	725	0.17	1.98	689.7	0.96	78.3
	d	1057.9	1.0	683	0.13	1.61	732.1	0.75	101.6
	e	1047.0	3.5	694	0.19	1.78	720.5	0.94	111.6
	f	1193.6	2.9	852	0.15	1.78	586.9	0.76	85.3
	Mean	1040.7	2.3	725	0.17	1.84	695.1	0.86	94.7
	S.D.	105.8	1.1	74	0.03	0.17	64.0	0.10	13.2
Healthy adult men	a	1116.5	2.8	779	0.14	2.04	641.8	0.82	109.3
	b	935.5	2.0	805	0.28	1.54	621.1	0.71	107.4
	c	935.0	2.7	827	0.28	2.67	604.6	0.83	137.8
	f	662.6	2.7	709	0.43	3.47	705.2	1.10	106.7
	g	788.2	2.4	592	0.20	1.65	844.6	1.18	105.0
	Mean	887.6	2.5	742	0.27	2.27	683.5	0.93	113.2
	S.D.	171.3	0.3	95	0.11	0.80	97.8	0.20	13.8
t-test (p value)		0.127	0.730	0.752	0.081	0.269	0.829	0.502	0.061

(Source: Study report of MCI186-10, page 45)

In addition, the sulfate and glucuronide conjugate PK data in plasma and urine measured with the two assays were generally consistent. The metabolites in plasma were measured in studies MCI186-10 (GC-MS), MCI186-14 and MCI186-E02 (LC-MS/MS). The sulfate was the major metabolite showing higher concentration than edaravone at all time points. The glucuronide showed lower concentration than edaravone at the beginning, then increased and showed higher concentration than edaravone. These trends were similar among the studies regardless of the bioanalytical methods.

The sulfate and glucuronide in urine were measured in studies MCI186-01, MCI186-10 (GC-MS), MCI186-14 and MCI186-E02 (LC-MS/MS). The data consistently showed that the predominant metabolite in urine was glucuronide, the sulfate was about 1/10 to 1/20 of the glucuronide, and only 1% or less parent drug was detected in urine

Overall, these results suggested that the bioanalytical methods are unlikely to have significant impact on the PK results obtained, and thus the results from all the 5 studies can be pooled together for the population PK analysis.

4.2 Clinical PK and/or PD Assessments

Five Phase 1 studies were conducted in Japan or European healthy subjects. The dosing regimens (infusion rate and duration, single and/or repeated doses, Table 3 in Appendix 4.1) and demographics (age and race, Table 18 in Appendix 4.3) varied among the studies. None of these dosing regimens represent the one tested in the Phase 3 trials for ALS (i.e., 60 mg infused over 60 min once daily). Please refer to Appendix 4.3 for a simulated PK profile of edaravone under the proposed dosing regimen. This was simulated using a population PK model which was developed using all the PK data from the 5 studies.

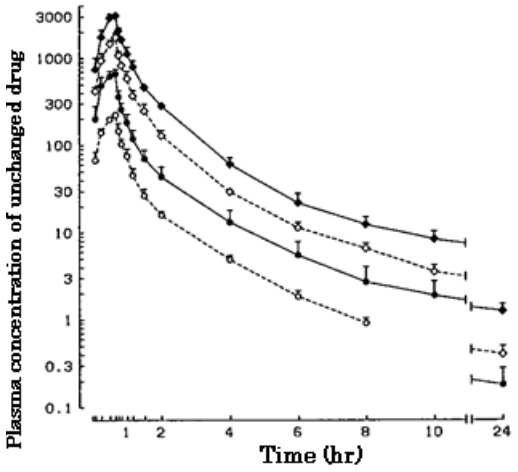
This section presents certain PK information from these individual studies in terms of single-dose and multiple-dose PK, dose proportionality, accumulation of edaravone after repeated doses, metabolite

concentrations compared with parent drug, urinary recovery, [redacted] (b) (4) biomarker measurements, and rationale of dose selection for Phase 3 trials in ALS.

1. Single-dose PK

The C_{max} of edaravone was reached by the end of infusion and then declined in a biphasic or triphasic manner (Figure 3).

Figure 3. Mean Plasma Concentrations of Unchanged Drug after Single Intravenous Infusion of Edaravone Injection to Japanese Healthy Male Adults (Mean value ± standard deviation, n = 5 for each dose).



(Source: Study report of MCI186-01, page 29)

Table 7. Elimination half-lives and AUCs after intravenous infusion of edaravone in Study MCI186-01

Dose level		2-compartment (0-8 hr)			3-compartment (0-24 hr)			
		$t_{1/2\alpha}$ (hr)	$t_{1/2\beta}$ (hr)	AUC (0-8 hr)[a] (ng•hr/mL)	$t_{1/2\alpha}$ (hr)	$t_{1/2\beta}$ (hr)	$t_{1/2\gamma}$ (hr)	AUC (0-24 hr)[a] (ng•hr/mL)
I (0.2 mg/kg, 40 min)		0.17 ± 0.03	1.45 ± 0.09	201 ± 14	—	—	—	—
II (0.5 mg/kg, 40 min)		0.15 ± 0.04	1.45 ± 0.18	581 ± 116	—	—	—	—
III (1.0 mg/kg, 40 min)		—	—	—	0.17 ± 0.03	0.85 ± 0.13	4.50 ± 0.68	1537 ± 153
IV (1.5 mg/kg, 40 min)		—	—	—	0.17 ± 0.07	0.81 ± 0.07	5.16 ± 0.31	3005 ± 236
V (1.0 mg/kg, 40 min, 7 days)	1st	—	—	—	0.14 ± 0.04	0.89 ± 0.06	6.01 ± 1.13	1474 ± 118
	7th	—	—	—	0.14 ± 0.03	0.78 ± 0.08	5.71 ± 0.29	1669 ± 88
VI (2.0 mg/kg, 3 hr)		—	—	—	0.12 ± 0.03	0.65 ± 0.04	4.38 ± 0.28	3717 ± 525

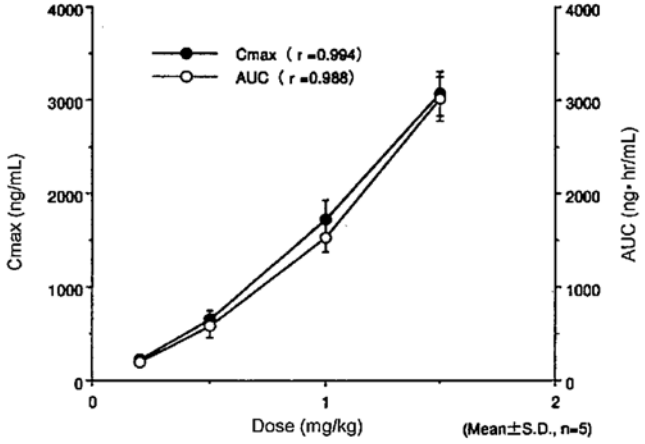
a): Calculated according to the trapezoid method (Mean ± S.D., n = 5)

—: Uncalculated

(Source: Study report of MCI186-01, page 26)

2. The AUC and C_{max} of edaravone increased more than dose proportionally (Figure 4).

Figure 4. Relationships between edaravone dose and C_{max} or AUC (Study MCI-186-01)



(Source: Study report of MCI186-01, page 29)

The nonlinearity was also observed in other studies. In Study MCl-186-E01, the AUC and C_{max} of edaravone increased by 5.2-fold when the dose increased from 0.6 mg/kg to 1.8 mg/kg (infused over 6 hrs, n = 10 for each group). In another study (MCI-186-E02) where edaravone was given as an IV bolus dose followed by a continuous infusion for 24 hrs, the clearance of edaravone remained similar between 0.05 mg/kg bolus + 0.125 mg/kg/hr and 0.1 mg/kg bolus + 0.25 mg/kg/hr (49.8 L/hr and 47.0 L/hr), but decreased to 37.6 L/hr after 0.2 mg/kg bolus + 0.5 mg/kg/hr dose.

Table 8. Dose-adjusted $AUC_{0-\infty}$ of unchanged edaravone in individual studies

Analytical method	Study	Treatment	Mean Body Weight (kg)	Mean Dose (mg/times)	Mean $AUC_{0-\infty}$ (ng·hr/mL)	$AUC_{0-\infty}$/Dose (ng·hr/mL/mg)
GC-MS	MCI186-01 Japanese	0.2 mg/kg/40 min, Single dose	64.1	13	201[b]	15.7
		0.5 mg/kg/40 min, Single dose	63.6	32	581[b]	18.3
		1.0 mg/kg/40 min, Single dose	64.7	65	1537[c]	23.8
		1.5 mg/kg/40 min, Single dose	69.9	105	3005[c]	28.7
		2.0 mg/kg/3 hr, Single dose	66.8	134	3717[c]	27.8
		1.0 mg/kg/40 min/day for 7 days, First dose, Multiple	66.6	67	1474[c]	22.1
		1.0 mg/kg/40 min/day for 7 days, Last dose, Multiple		67	1669[c]	25.1
	MCI186-10 Japanese Healthy adult	0.5 mg/kg/30 min × 2 times/day for 2 Days, Multiple dose	65.6	33	742	22.6
	Japanese Healthy elderly		64.1	32	725	22.6
	MCI186-E01 Caucasian	0.1 mg/kg/hr for 6hr, Single dose[a]	71.30	43	463	10.8
		0.3 mg/kg/hr for 6hr, Single dose		128	2447	19.1
LC-MS/MS	MCI186-14 Japanese	240 mg/48 hr, Single dose	64.1	240	4560	19.0
	MCI186-E02 Caucasian	0.05 mg/kg bolus (3 min) + 0.125 mg/kg/hr infusion over23 hours 57 min, Single dose	71.94	219	4744	21.7
		0.1 mg/kg bolus (3 min) + 0.25 mg/kg/hr infusion over 23 hours 57 min, Single dose		438	9945.9	22.7
		0.2 mg/kg bolus (3 min) + 0.50 mg/kg/hr infusion over 23 hours 57 min, Single dose		876	24135.5	27.6

[a] Data was excluded from PPK modeling as significant numbers of samples showed below the lower limit of quantitation.

[b] AUC_{0-8h}

[c] AUC_{0-24h}

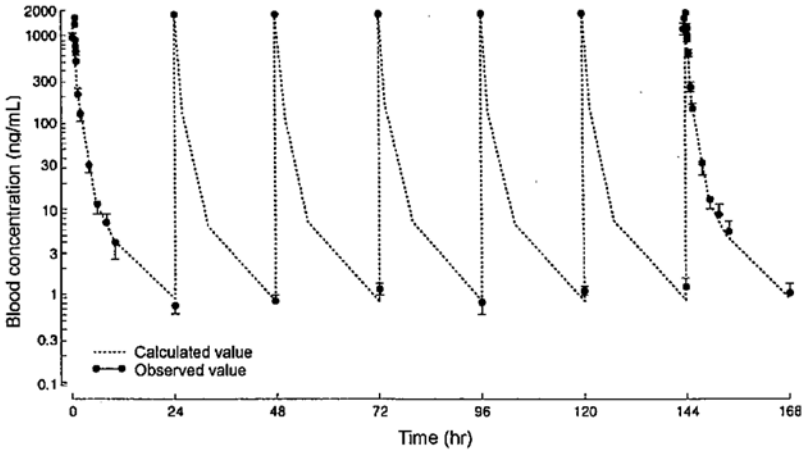
(Source: response to information request submitted on January 19. 2017, sequence 0049)

One of the possible explanations for nonlinear PK could be saturation of its metabolism. However, the Km values for the formation of edaravone glucuronide in human liver microsomes and human kidney microsomes were measured as 156 - 240 µM and 80 - 183 µM, respectively. The Km of edaravone glucuronidation in human kidney homogenates was 136.9 µM. Thus, nonlinear PK of edaravone may not be attributed to saturation of its glucuronidation, since the C_{max} of edaravone at therapeutic dose (about 6 µM) is far below the Km value for its glucuronidation. The Km of edaravone sulfation is unknown. The applicant attempted to measure the metabolism from edaravone to its sulfate conjugate using human kidney homogenate but could not detect the sulfate metabolite.

3. Multiple-dose PK

There was no change in PK of edaravone after repeated doses. No accumulation of edaravone was observed after multiple dosing (Studies MCI186-01 and MCI186-10).

Figure 5. Time-course of plasma edaravone concentrations in multiple dosing (1.0 mg/kg, 40 min, 7 days) (Mean ± S.D, n = 5)



(Source: Study report of MCI186-01, page 32)

4. Metabolites concentrations in plasma

The ratios of sulfate or glucuronide conjugates to the parent drug varied among studies. Nevertheless, sulfate conjugate is the predominant moiety in the plasma. The terminal half-life of sulfate and glucuronide conjugates were determined only in Study MCI186-E02 as 2 - 2.8 hrs and 2.2 -2.8 hrs, respectively, shorted than that of edaravone (5.4 - 7 hrs).

In Study MCI186-10, after the first dose, the ratios of sulfate conjugate to parent drug were 2.5 or 2.1 at $C_{30\ min}$ (the end of infusion) and increased to 17.6 or 27.8 at C_{12hr} (before the next dose), in young adults and elderly subjects, respectively. In comparison, the ratios of glucuronide conjugate to parent drug were 0.6 or 0.4 at $C_{30\ min}$ (the end of infusion) and increased to 1.6 or 5.2 at C_{12hr} (before the next dose), in young adults and elderly subjects, respectively.

Table 9. Plasma Concentrations of Metabolites after Repeated Infusion of Edaravone Injection (at a Twice Daily Dose of 0.5 mg/kg/30 min for 2 Days) in Japanese Healthy Male Adults and Elderly Subjects

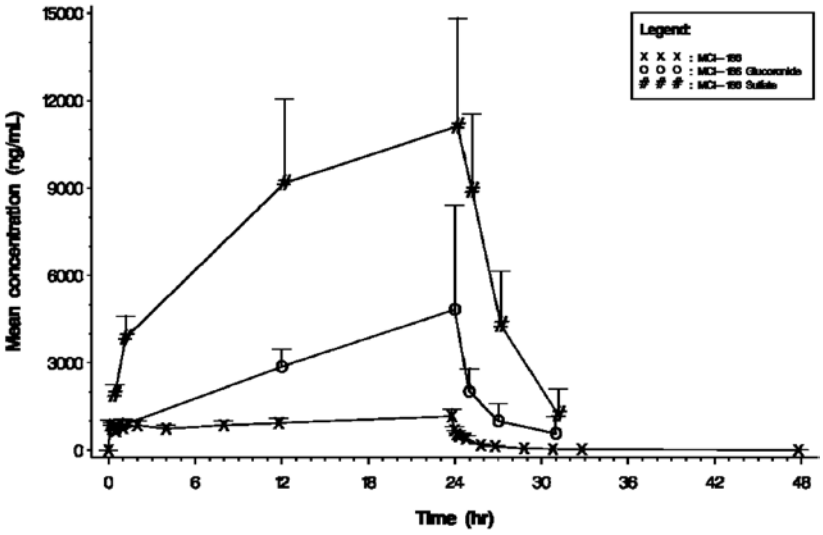
	Plasma concentrations of metabolites (ng/mL)			
	Healthy adult subjects		Elderly subjects	
Time	Sulfate	Glucuronide	Sulfate	Glucuronide
0.5 hr after first dose	2174 ± 116	516 ± 406	2151 ± 821	378 ± 152
4 hr after first dose	462 ± 59	56 ± 24	549 ± 228	158 ± 73
Just before 2nd dose	44 ± 6	4 ± 4	64 ± 39	12 ± 6
0.5 hr after 4th dose	2477 ± 97	561 ± 228	2154 ± 385	646 ± 226
12 hr after 4th dose	66 ± 12	13 ± 9	75 ± 44	20 ± 11

Mean value ± standard deviation, n = 5 in each age group.

(Source: Summary of clinical pharmacology, page 37. Originally from Study MCI186-10)

In another study MCI186-E02, the AUC ratios of sulfate conjugate to the parent drug were 10.9, 10.1, and 9.7 across three dosing groups. The C_{max} ratios were similar, about 9.5. The AUC ratios of glucuronide conjugate to edaravone remained similar, 3.0, 3.6, and 3.2, for the three dose groups. But the C_{max} ratios increased along with doses, from 2.9 to 4.4.

Figure 6. Arithmetic mean (+ SD) concentration-versus-time curves for group 2 (0.2 mg/kg + 0.50 mg/kg/h); PK population, edaravone, glucuronide and sulfate metabolite (N=10);



(Source: Study report of MCI186-E02, page 71)

No PK data were obtained for the dosing regimen of the Phase 3 trials (also the proposed dosing regimen of edaravone in labeling, i.e., 60 mg infused over 60 min). The dosing regimen in Study MCI186-10 and the one of Study MCI186-E02 presented above may be the ones closer to the proposed dosing regimen. Thus, the sulfate conjugate after the proposed dosing regimen is roughly estimated as 5 times of the parent drug (i.e., the ratio of sulfate/parent drug at 1hr after dosing of the 0.2 mg/kg bolus + 0.5 mg/kg/hr infusion group).

5. Urinary recovery of edaravone and its metabolites

The extents of urinary recovery varied among the 5 studies and were > 70% of administered dose except Study MCI186-14 where the cumulative excretion of edaravone and its metabolites in urine accounted for 59% of the dose. But, the overall findings were similar, i.e., only a small amount of administered dose (1% or less) was recovered as parent drug in urine. In contrast to the compositions in plasma, the glucuronide conjugate is the predominant moiety in urine.

Table 10. Urinary excretion rates (%) of edaravone, its sulfate and glucoronate conjugates

Dose level		MCI-186	Sulfate	Glucuronate	Total
I: 0.2 mg/kg		0.56 ± 0.11	5.61 ± 3.87	77.88 ± 5.86	84.04 ± 2.49
II: 0.5 mg/kg		0.98 ± 0.51	12.50 ± 10.75	68.64 ± 11.26	82.12 ± 3.93
III: 1.0 mg/kg		0.68 ± 0.13	6.58 ± 1.69	83.17 ± 4.36	90.43 ± 4.38
IV: 1.5 mg/kg		0.83 ± 0.14	7.11 ± 4.54	78.06 ± 9.25	86.01 ± 5.95
V: 1.0 mg/kg	Day 1	—	6.41 ± 1.79	70.09 ± 10.76	76.49 ± 10.27
	Day 2	—	6.20 ± 1.92	77.29 ± 3.17	83.49 ± 3.10
	Day 3	—	6.39 ± 1.71	75.91 ± 2.99	82.30 ± 3.31
	Day 4	—	5.84 ± 1.63	75.98 ± 3.03	81.82 ± 1.89
	Day 5	—	5.99 ± 1.48	76.47 ± 5.55	82.46 ± 5.45
	Day 6	—	5.83 ± 1.71	74.73 ± 2.99	80.56 ± 3.48
	Day 7	0.98 ± 0.08	6.61 ± 1.60	77.96 ± 4.24	85.55 ± 5.06
VI: 2.0 mg/kg		0.82 ± 0.17	13.16 ± 14.23	72.97 ± 11.19	86.94 ± 4.35

—: Unmeasured
(Mean ± S.D., n = 5)

(Source: Study report of MCI186-01, page 27)

The urinary composition of edraravone/its metabolites in European subjects were similar to that in Japanese subjects. This suggests that there is no significant difference in edaravone PK between the Japanese and EU/US populations.

Table 11. Urinary Excretion (% of Dose: Ae%0-48h) of Unchanged Drug, Sulfate, and Glucuronide During 24-hour Continuous Intravenous Infusion of Edaravone 0.125, 0.25, and 0.5 mg/kg/hr in Caucasian Healthy Male and Female Adults

	Urinary excretion (% of dose: $Ae\%_{0-48h}$)			
Subject	**Unchanged drug**	**Sulfate**	**Glucuronide**	**Total**
Cohort 3: 0.125 mg/kg/hr edaravone (incorporating a 3-min bolus dose of 0.05 mg/kg/hr)				
N	10	10	10	10
Mean	0.696	3.895	92.280	96.871
SD	0.305	2.915	8.838	8.610
Median	0.615	3.452	89.575	94.189
Minimum	0.39	0.86	82.83	88.99
Maximum	1.47	8.74	108.92	112.18
Cohort 1: 0.25 mg/kg/hr edaravone (incorporating a 3-min bolus dose of 0.1 mg/kg/hr)				
N	10	10	10	10
Mean	4.038	5.269	83.186	92.493
SD	11.079	4.791	24.652	13.785
Median	0.511	4.515	85.529	92.139
Minimum	0.38	1.05	22.11	62.90
Maximum	35.57	17.65	106.49	108.19
Cohort 2: 0.5 mg/kg/hr edaravone (incorporating a 3-min bolus dose of 0.2 mg/kg/hr)				
N	10	10	10	10
Mean	0.706	9.948	86.366	97.020
SD	0.289	5.960	19.130	20.475
Median	0.677	9.484	85.390	97.204
Minimum	0.12	2.18	62.06	64.76
Maximum	1.14	23.50	128.30	136.19

(Source: Summary of clinical pharmacology, page 50. Originally from Study MCI186-E02)

Results from *in vitro* experiments suggested that the sulfate conjugate may be deconjugated in human kidney and then reconjugated to form the glucuronide conjugate. Both sulfate and glucuronide conjugates showed low membrane permeability in Caco-2 cells. The sulfate metabolite was a substrate of uptake transporters, OAT1 and OAT3 (Km values were 10.8 µM and 15.1 µM, respectively), while the glucuronide conjugate was not. Thus, sulfate conjugate in plasma may be taken up into kidney proximal tubular cells.

Experiments using human kidney homogenates showed that the sulfatase activity (responsible for degradation of sulfate conjugate) using edaravone sulfate as the substrate was comparable to that using a positive control substrate, 7-Hydroxycoumarin (1055 pmol/min/mg protein vs. 1264 pmol/min/mg protein). In contrast, the sulfotransferase activity using edaravone as the substrate cannot be determined as sulfate conjugate was not detected in the homogenate preparations. Thus, the environment of kidney cells may favor the conversion of edaravone sulfate to the parent drug.

In contrast, the activity of β-glucuronidase (responsible for degradation of glucuronide conjugates) in human kidney homogenates, as measured by 7-Hydroxycoumarin glucuronide, was low. The β-glucuronidase activity for deconjugation of edaravone glucuronide was 3.36 pmol/min/mg protein. The UGT activity of the kidney homogenates using edaravone as substrate was 14.8 pmol/min/mg protein. Hence, the enzyme activities of kidney cells favor the formation of edaravone glucuronide.

Similar results were obtained from human kidney sf9 preparations.

Table 12. UDP-glucuronyltransferase (UGT), sulphotransferase (ST), β-glucuronidase (βG) and sulfatase (S) activities in kidney S9 of rat, dog, and human

Species	Activity (pmol/min/mg protein)			
	UGT	ST	βG	S
Rat (n=3)	ND	93 ± 26	11 ± 4.3	ND
Dog (n=2)	ND	612	54	9
Human (n=3)	55 ± 18	8.2	7.6 ± 1.5	83 ± 43

Each value represents the mean (± S.D.)

ND: Not detected

(Source: report for study s-29, page 16)

When edaravone sulfate metabolite was added to human kidney S9 in the presence of uridine 5'diphosphoglucuronic acid (UDPGA), the metabolite decreased with the progress in reaction time and the parent drug and edaravone glucuronide were produced. There was neither an increase in edaravone nor production of edaravone sulfate conjugate when the glucuronide conjugate was added to kidney sf9 preparations even in the presence of adenosine 3'-phosphate 5'-phosphosulfate (PAPS).

The glucuronide conjugate was a substrate of efflux transporter MRP4 but not BCRP. In contrast, the sulfate conjugate was transported by BCRP but not MRP4. Thus, MRP4 and BCRP may account for excretion of glucuronide and sulfate conjugates of edaravone into urine, respectively.

(b) (4)

[redacted]

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

7. Biomarker Assessment

In Study MCI186-10, lipid peroxide concentrations (reflecting oxidative stress) were measured at 30 min before the first administration of edaravone and on the next day of completion of edaravone dosing. There was no significant difference in lipid peroxide concentrations in healthy young adults or elderly subjects. Free fatty acid in blood was also examined using $C_{16:1}$ as the tissue injury index. Edaravone administration did not have effect on free fatty acid ($C_{16:1}$) concentrations in blood, either.

The Phase 2 trial (MCI186-12) investigated 3NT (3-Nitrotyrosine) levels as an oxidative stress marker. The 30-mg group and 60-mg group demonstrated 3NT decreased below or close to the detection limit at the end of administration of Cycle 6.

Table 15. 3-Nitrotyrosine (ng/mL) levels in patients with ALS in cerebral spinal cord fluid (CSF)

Administration group	N	Before administration at Cycle 1		At the end of administration at Cycle 1		At the end of administration at Cycle 6	
30 mg group	5	Mean (SD)	0.70 (0.81)	Mean (SD)	0.39 (0.33)	Mean (SD)	0.00 (-)[a]
		Med (Min, Max)	0.588 (0, 1.937)	Med (Min, Max)	0.405 (0, 0.87)	Med (Min, Max)	0[a] (0, 0)[a]
60 mg group	14	Mean (SD)	1.02 (1.32)	Mean (SD)	0.75 (1.10)	Mean (SD)	0.07 (0.23)[b]
		Med (Min, Max)	0.657 (0, 4.783)	Med (Min, Max)	0.2755 (0, 4.035)	Med (Min, Max)	0[b] (0, 0.793)[b]

[a] N = 4.
[b] N = 12.

(Source: Summary of clinical pharmacology, page 69, originally from Study MCI186-12)

8. Rationale of dose selection for Phase 3 trials

Per the applicant, for treatment of acute ischemic stroke (AIS), a Japanese Phase 2b trial investigated 10 mg/30 min, 30 mg/30 min, and 45 mg/30 min of edaravone IV infusion twice a day (Study MCI186-05). There was no difference in efficacy between 30 mg/30 min and 45 mg/30 min. Thus, 30 mg/30 min

twice a day (60 mg as daily dose) was selected for the Phase 3 study of AIS and later on was approved in Japan.

Study MCI186-12 was a Phase 2, open-label, exploratory study in patients in any stage of ALS who received edaravone for 6 cycles. The first group of subjects was administered a dose of 30 mg/day (once daily, half of the daily dose for AIS, to 5 subjects), and then the second group of subjects was administered 60 mg/day (once daily, n = 14). The effect of edaravone was shown by reduction in levels of the biomarker, 3NT in CSF (Table 15). A beneficial effect at 60 mg as assessed by ALSFRS-R was observed. Thus, the applicant chose 60 mg/day (IV infusion over 60 minutes) for all the Phase 3 trials in ALS patients.

4.3 Population PK and/or PD Analyses

The purpose of the analysis was to investigate whether there are PK differences of edaravone (MCI-186) in Japanese and non-Japanese (United States [US]/Europe [EU]) subjects and to further characterize the PK of edaravone through population modeling.

1. Data

Study Designs and Populations

Data were obtained from the studies described in **Table** 16.

Table 16. Studies Included in the Population Pharmacokinetic Analysis

Study Number/ Phase	Study Title	Participants (Race)	Duration of Dosing	Number of Subjects[a]	Number of Subjects Used for Analysis
MCI-186-J01/ Phase 1	Phase 1 Clinical Trial of MCI-186 (Edaravone, 3-methyl-1-phenyl-2-pyrazolin-5-one) in Healthy Volunteers: Safety and Pharmacokinetics of Single and Multiple Dose Administration	Healthy volunteers (Japanese)	1 day, 1 dose except Dose Group 5 7 days, 7 doses	n = 30 active treatment n = 12 placebo	30
MCI-186-J10/ Phase 3	Continuous Administration Study for MCI-186 in Healthy Elderly Subjects and Healthy Adult Men	Healthy volunteers/ Healthy elderly volunteers (Japanese)	2 days 4 doses	n = 10 active treatment n = 4 placebo	10
MCI-186-J14/ Phase 3	Clinical Pharmacology Study to Evaluate Pharmacokinetic Profile of MCI-186 (Edaravone) Administered by Continuous Intravenous Drip Infusion for 48 Hrs in Healthy Japanese Male Volunteers	Healthy volunteers (Japanese)	2 days 1 dose	n = 8 active treatment[b]	7
MCI-186-E01/ Phase 1	A Phase 1, Double-blind, Placebo-controlled and Ascending-dose Intravenous Study to Determine the Safety, Tolerability and Pharmacokinetic Profiles of MCI-186 in Healthy, Male and Female Caucasian Volunteers	Healthy volunteers (Caucasian)	1 day 1 dose	n = 20 active treatment n = 4 placebo	20
MCI-186-E02/ Phase 1	A Phase 1, Double-blind, Placebo-controlled, Ascending Dose Clinical Study Investigating the Pharmacokinetics, Safety and Tolerability of a Bolus and Subsequent Infusion, of a New Formulation of Edaravone in Male and Female Caucasian Subjects	Healthy male volunteers/ Healthy female volunteers (Caucasian)	1 day 1 dose	n = 33 active treatment[c] n = 13 placebo	30

[a] Placebo subjects were excluded from the development of the population pharmacokinetic model for MCI-186.
[b] One subject was excluded from the development of the population pharmacokinetic model for MCI-186, due to malfunction of the perfusion pump.
[c] Four subjects (3 active treatment and 1 placebo) were excluded from the development of the population pharmacokinetic model for MCI-186 due to infusion failure.

Source : Table 1 on Page 53 in study report.

Dosing Regimens

Dosing regimens for MCI-186 are described in **Table** 3.

Pharmacokinetic Sampling Strategies

Pharmacokinetic sampling strategies for MCI-186 are described in **Table** 17.

Table 17. Pharmacokinetic Sampling Times Stratified by Study and Treatment Group

Study	Treatment Group	Number of Doses	Scheduled Sample Times Relative to Start of Infusion (h)
MCI-186-J01	0.2, 0.5, 1.0, and 1.5 mg/kg 40-minute infusion	1	0, 0.083, 0.25, 0.5, 0.67, 0.75, 0.83, 1.0, 1.167, 1.5, 2, 4, 6, 8, 10, and 24
	1.0 mg/kg 40-minute infusion	1 and 7	0, 0.25, 0.5, 0.67, 0.75, 0.83, 1.0, 1.167, 1.5, 2, 4, 6, 8, 10, and 24
		2, 3, 4, 5, and 6	0 and 0.67
	2.0 mg/kg 3-hour infusion	1	0, 0.5, 1, 2, 2.5, 3.0, 3.083, 3.167, 3.33, 3.5, 4, 6, 8, 10, and 24
MCI-186-J10	0.5 mg/kg twice daily	1	0, 0.25, 0.5, 0.67, 1.0, 2, 4, and 8
		2 and 3	0 and 0.5
		4	0, 0.5, and 12
MCI-186-J14	240 mg 48-hour infusion	1	0, 0.5, 1.0, 2, 4, 6, 9, 15, 24, 30, 36, 48, 48.5, 48.167, 48.33, 48.5, 49, 50, 51, 53, 55, 57, and 72
MCI-186-E01	0.6 and 1.8 mg/kg 6-hour infusion	1	0, 0.5, 1.0, 2, 4, 6, 6.083, 6.167, 6.33, 6.5, 7, 7.5, 8, 10, 12, 14, 16, 24, 36, and 48
MCI-186-E02	0.1 + 0.25, 0.2 + 0.50, and 0.05 + 0.125 mg/kg 0.05- + 23.95-hour infusions	1	0, 0.1167, 0.25, 0.5, 1.0, 2, 4, 8, 12, 24, 24.167, 24.33, 24.5, 25, 26, 27, 29, 31, 33, and 48

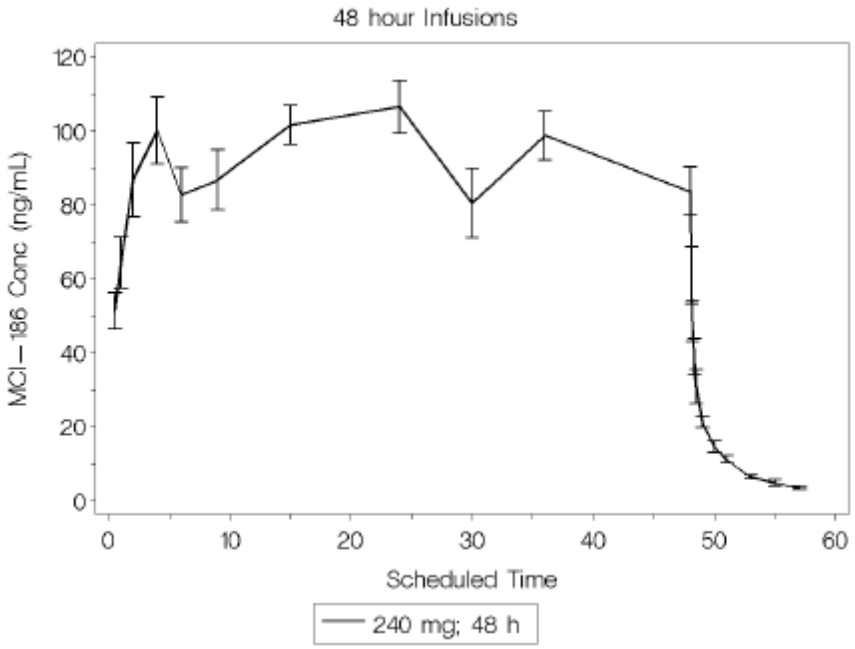
Source : Table 3 on Page 55 in study report.

2. Sponsor's Analysis

Structural Model Building

Population modeling was performed using the computer program NONMEM® (Version 7, Level 3.0.16). The first-order conditional estimation with interaction method was used during all stages of the model development process unless convergence problems were encountered or the interaction option was deemed unnecessary by virtue of the choice of residual variability (RV) model. The exploratory data analysis showed that MCI-186 concentrations declined in a multi-phasic manner post infusion and plots of dose-normalized concentrations indicated that the PK of MCI-186 may exhibit nonlinearity. Concentration-time profiles during longer infusions (24 to 48 hours) also exhibited a multi-peak behavior during the infusion (**Figure** 7).

Figure 7. Mean ± Standard Deviation Plots of MCI-186 (Edaravone) Concentration Versus Time Since Start of Infusion for the 48-hour Infusion Group.



The PK analysis showed that, among the various models evaluated (**Figure** 8), a 3-compartment model with Michaelis-Menten plus linear elimination and a 24-hour fluctuation in the maximum nonlinear elimination rate best described the data. A 24-hour fluctuation in Vmax was included in the model because the observed data exhibited fluctuations in the 24-hour and 48-hour infusions. The equation is shown below.

$$Vmax = VMM + VMM \cdot VMA \cdot sin\left(\frac{2\pi}{24} \cdot t\right)$$

Where:

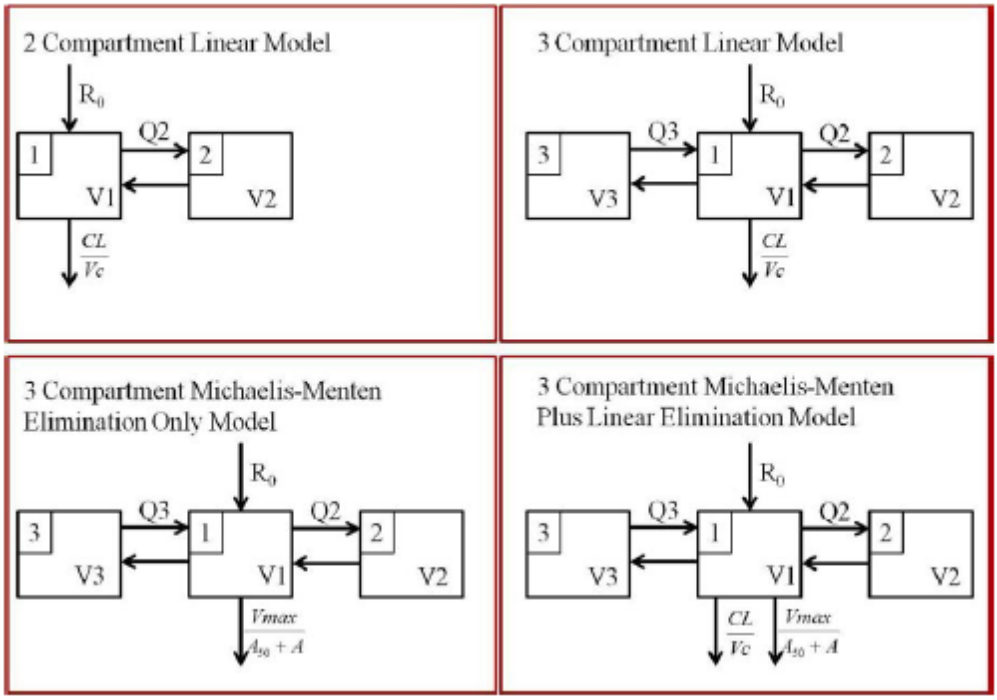
$Vmax$ is the maximum nonlinear elimination rate;

VMM is the midpoint of $Vmax$;

VMA is the amplitude of $Vmax$ expressed as a fraction of VMM; and

t is continuous time (h).

Figure 8. Model Diagrams



Source : Figure 7 on page 94 in study report.

Covariate Analysis

The following covariates were evaluated for their ability to explain variability in the PK model parameters:

- Age, years
- Weight, kg
- Sex (0 = male, 1 = female)
- Race (0 = Japanese, 1 = non-Japanese [US/EU])

All covariates were assumed to remain constant throughout the studies and values collected at the screen or baseline visit were used.

Clinical relevance of statistically significant covariate effects was assessed through the summarization and/or graphical representation of subject-specific model-predicted exposure measures versus covariates.

Comparing anticipated MCI-186 (Edaravone) exposures in Japanese and non-Japanese (US/EU) patients with ALS

Simulations were performed to compare anticipated MCI-186 exposures in Japanese and non-Japanese (US/EU) patients with ALS.

A virtual population of 2,000 ALS patients (1,000 Japanese and 1,000 non-Japanese) was generated by randomly assigning the sex, age, and weight based upon the race-specific distributions. .

Three dosing regimens were selected and simulated for a virtual ALS population of Japanese and non-Japanese (US/EU) patients (total of 2,000 patients). Summary statistics and boxplots of exposures stratified by race were generated for each dosing regimen.

Results

The final analysis dataset had a total of 1,519 MCI-186 concentration records from 86 subjects. Approximately 55% of the population was Japanese and approximately 23% of the population was female. Subjects were 20 to 71 years of age with an average age of 46 years and a mean weight (SD) of 68.9 (9.13) kg.

Table 18. Summary Statistics of Subject Descriptors of the Final Analysis Dataset Stratified by Study

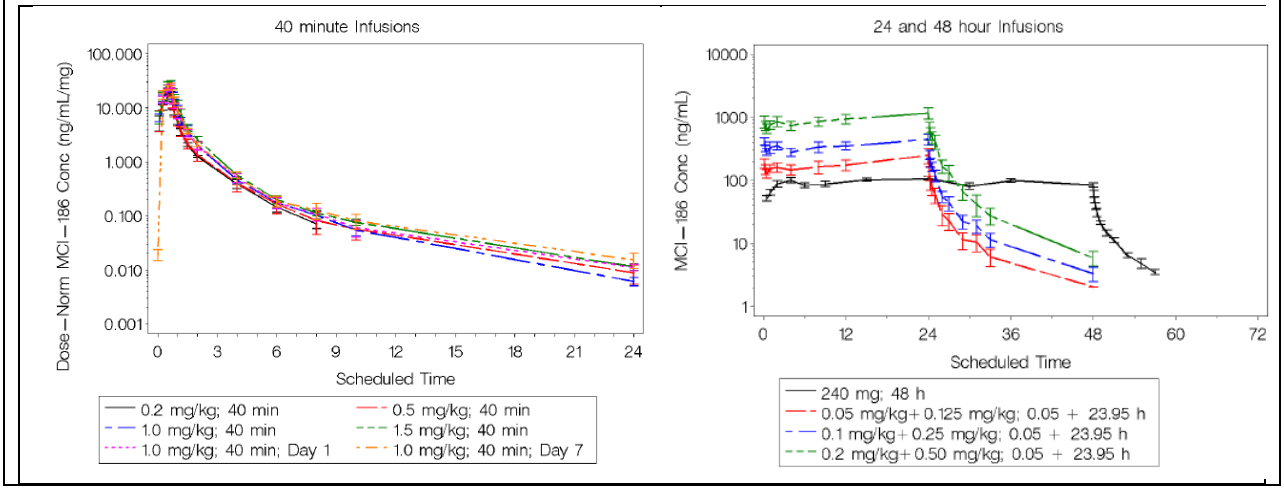
Subject Characteristic		MCI-186-E01	MCI-186-E02	MCI-186-J01	MCI-186-J10	MCI-186-J14	Overall
Baseline Age (y)	Mean (SD)	59.1 (5.3)	61.4 (5.5)	30.5 (5.6)	48.5 (21.6)	23.3 (3.1)	45.8 (17.4)
	Median	58.5	62.0	28.5	50.0	23.0	51.5
	Min, Max	52, 68	51, 70	24, 44	25, 71	20, 28	20, 71
	n	10	29	30	10	7	86
Baseline Weight (kg)	Mean (SD)	72.98 (11.50)	72.97 (8.80)	66.34 (7.48)	63.71 (6.33)	64.06 (8.87)	68.86 (9.13)
	Median	72.65	72.10	66.05	62.35	62.70	68.60
	Min, Max	49.9, 88.6	59.3, 99.9	53.7, 85.0	56.8, 74.2	50.9, 75.4	49.9, 99.9
	n	10	29	30	10	7	86
Race, n (%)	Japanese	0 (0.0)	0 (0.0)	30 (100.0)	10 (100.0)	7 (100.0)	47 (54.7)
	Non-Japanese (US/EU)	10 (100.0)	29 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	39 (45.3)
Sex, n (%)	Male	5 (50.0)	14 (48.3)	30 (100.0)	10 (100.0)	7 (100.0)	66 (76.7)
	Female	5 (50.0)	15 (51.7)	0 (0.0)	0 (0.0)	0 (0.0)	20 (23.3)

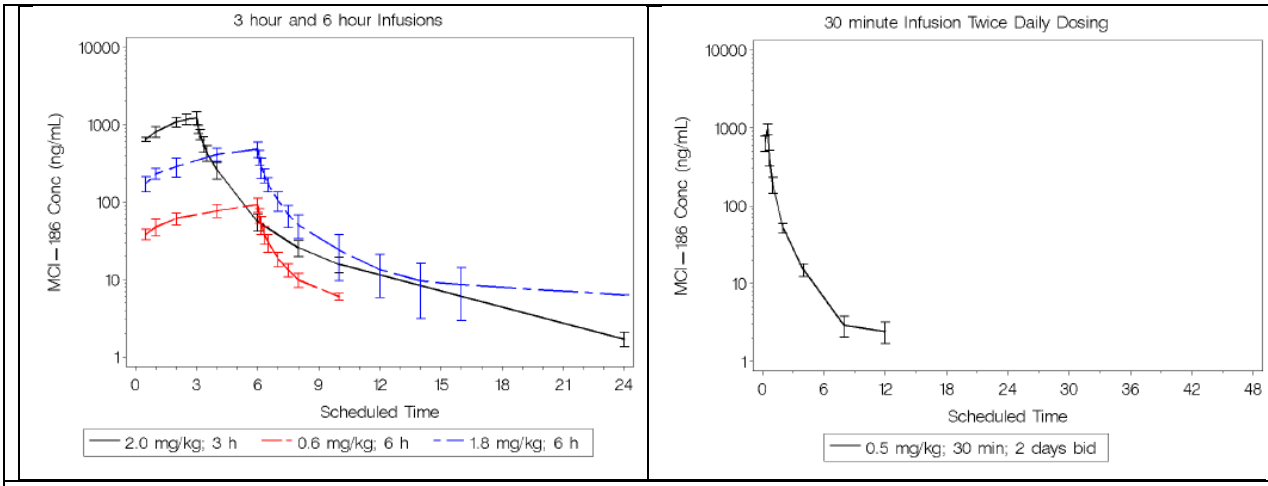
Abbreviations: EU, Europe; Max, maximum; Min, minimum; n, number of subjects; SD, standard deviation; US, United States.

Source: Table 8 on page 60 in study report

Figure 9 shows the edaravone (MCI-186) concentration-time profile for various dosing regimens..

Figure 9. Mean +/- Standard Deviation Plots of MCI-186 (Edaravone) Concentration Versus Time Since Start of Infusion Stratified by Treatment Group Displayed on a Log-Linear Scale

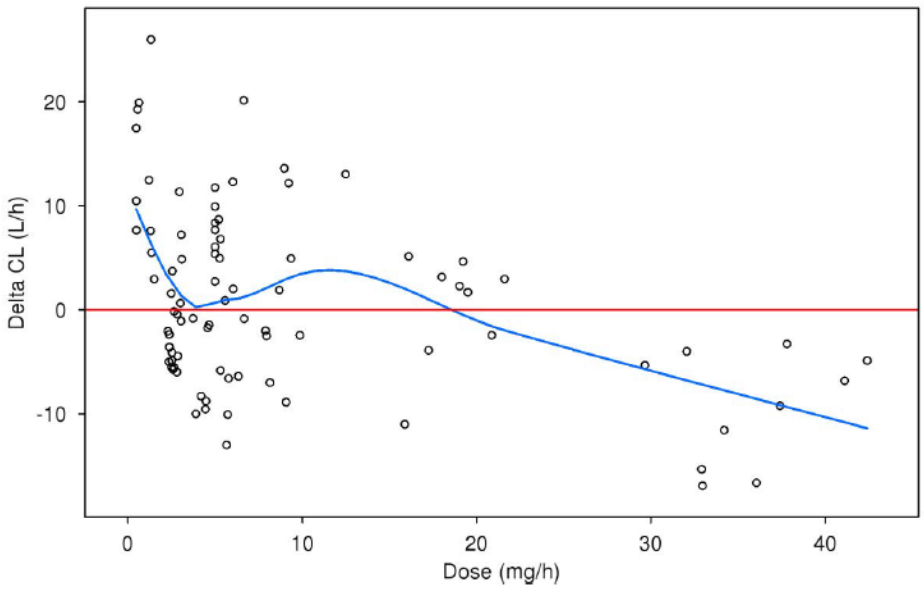




Source : Figure 3, 4 and 5 on pages 89-92 in study report.

Figure 11 show the comparison of goodness of fit plot (population predicted versus observed concentrations; stratified by study) between a model with assumption of elimination process being linear and linear+nonlinear+fluctuations in Vmax. Plot of delta clearance versus dose, as shown in **Figure** 10, suggested the need for including non-linearity component in the model.

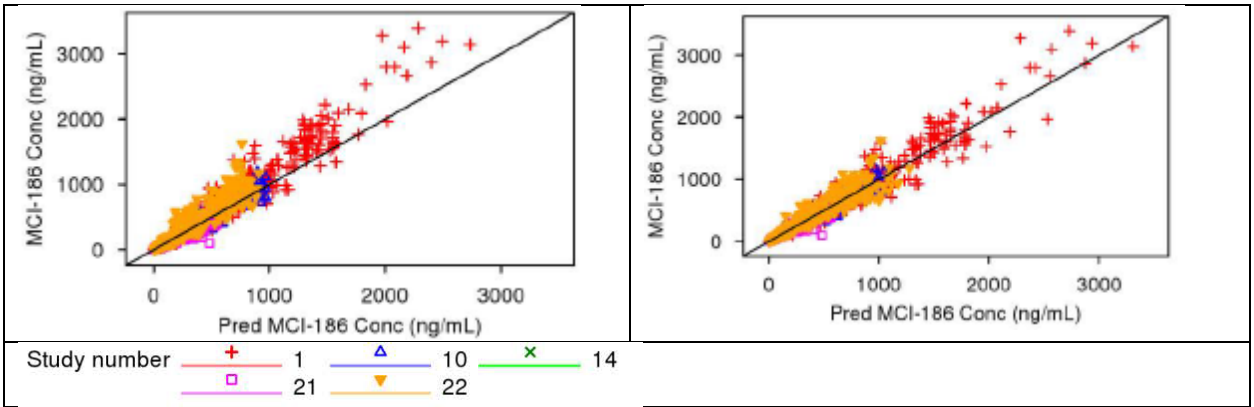
Figure 10. Plot of Delta-Clearance Versus Dose (mg/h) for the MCI-186 (Edaravone) Base 3-Compartment Linear Model. The line represents a smoothing spline fit to the data



Source : Figure 9 on page 96 in study report.

Figure 11 shows that the model with assumption of elimination process being linear+nonlinear+fluctuations in Vmax best describes the data. The underprediction at higher concentrations as seen in the left graph (model with linear elimination) is less apparent in the right graph (model with linear+nonlinear+fluctuating maximum nonlinear elimination) as shown in **Figure 11**.

Figure 11. Goodness-of-fit Plots for the MCI-186 (Edaravone) (Left) Base 3-Compartment Linear Model (Right) Base 3-Compartment Model With Michaelis-Menten Plus Linear Elimination and Fluctuating Maximum Nonlinear Elimination Stratified by Treatment Group.



Source : Figure 8 on page 95 and Figure 13 on page 100 in study report. Study 1(MCI-186-J01), Study 10(MCI-186-J10), Study 14(MCI-186-J14), Study 21(MCI-186-E01), Study 22(MCI-186-E02).

During the forward selection procedure, race and sex were found to be significant predictors of CL, V2, and V3. The addition of race and sex reduced the interindividual variability (IIV) in CL, V2, and V3 by 5.5%, 28.2%, and 8.2%, respectively. Univariate stepwise backward elimination proceeded after evaluation of the full multivariable model. Only the effect of race on V2 was statistically significant ($p < 0.001$) and retained in the model.

Table 19 shows the estimates of parameters from the final population pharmacokinetic model.

Table 19. Parameter Estimates and Standard Errors From the Final MCI-186 (Edaravone) Population Pharmacokinetic Model

	Final Parameter Estimate		Interindividual Variability / Residual Variability	
Parameter	**Typical Value**	**%SEM**	**Magnitude**	**%SEM**
CL: Clearance (L/h)	23.0	8.26	20.7 %CV	22.9
V1: Central Volume of Distribution (L)	14.7	4.44	23.4 %CV	26.8
Q2: Intercompartmental Clearance (L/h)	4.79	5.71	NE	NE
V2: Peripheral Volume of Distribution (L)	32.6	6.40	16.0 %CV	26.7
V2: Proportional Shift for Non-Japanese	0.262	21.9		
Q3: Intercompartmental Clearance 2 (L/h)	26.8	3.14	NE	NE
V3: Peripheral Volume of Distribution 2 (L)	25.1	3.49	26.0 %CV	22.3
A50: Amount to Achieve 50% of VMM(mg)	6.84	19.9	NE	NE
VMM: Midpoint Maximum Elimination Rate (mg/h)	17.9	17.9	NE	NE
VMMF: Fractional Amplitude of VMM (Unitless)	0.174	18.9	NE	NE
Log RV for Study MCI-186-J01, J14 & E02	0.0199	7.74	0.141 SD	NA
Log RV for Study MCI-186-J10	0.0665	20.4	0.258 SD	NA
Log RV for Study MCI-186-E01	0.0492	34.0	0.222 SD	NA
Minimum Value of the Objective Function = -3482.919				

Abbreviations: %CV, coefficient of variation expressed as a percentage; NA, not applicable; NE, not estimated; RV, residual variability; SD, standard deviation; %SEM, standard error/parameter estimate × 100.

$$Vmax = VMM + VMM \cdot VMMF \cdot sin\left(\frac{2\pi}{24} \cdot t\right)$$

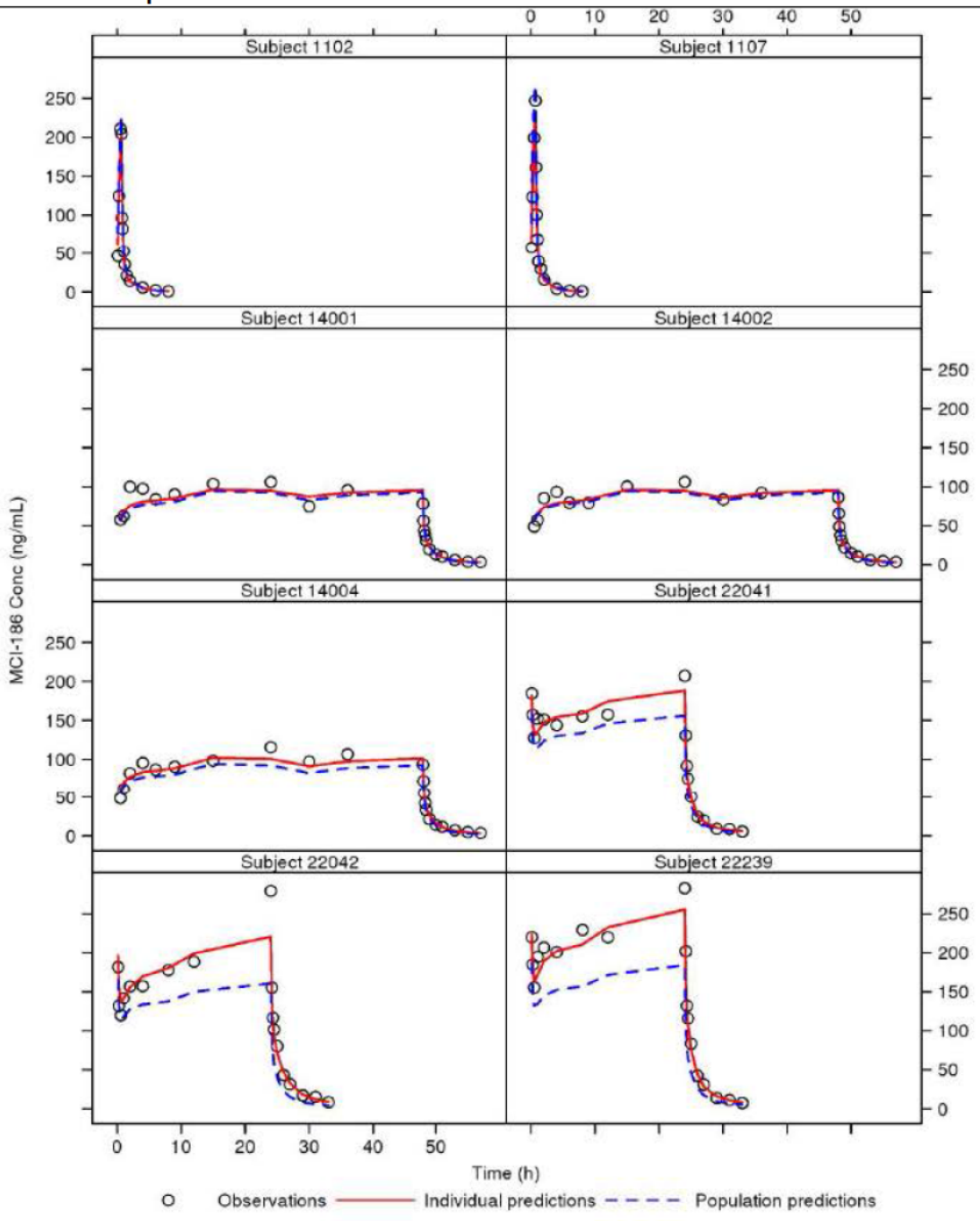
Where:

$Vmax$ is the maximum nonlinear elimination rate;
VMM is the midpoint of $Vmax$;
$VMMF$ is the amplitude of $Vmax$ expressed as a fraction of VMM; and
t is continuous time (h).

Source : Table 21 on page 73 in study report.

Figure 12 shows observed, population predicted and individual predicted concentration versus time in representative patients.

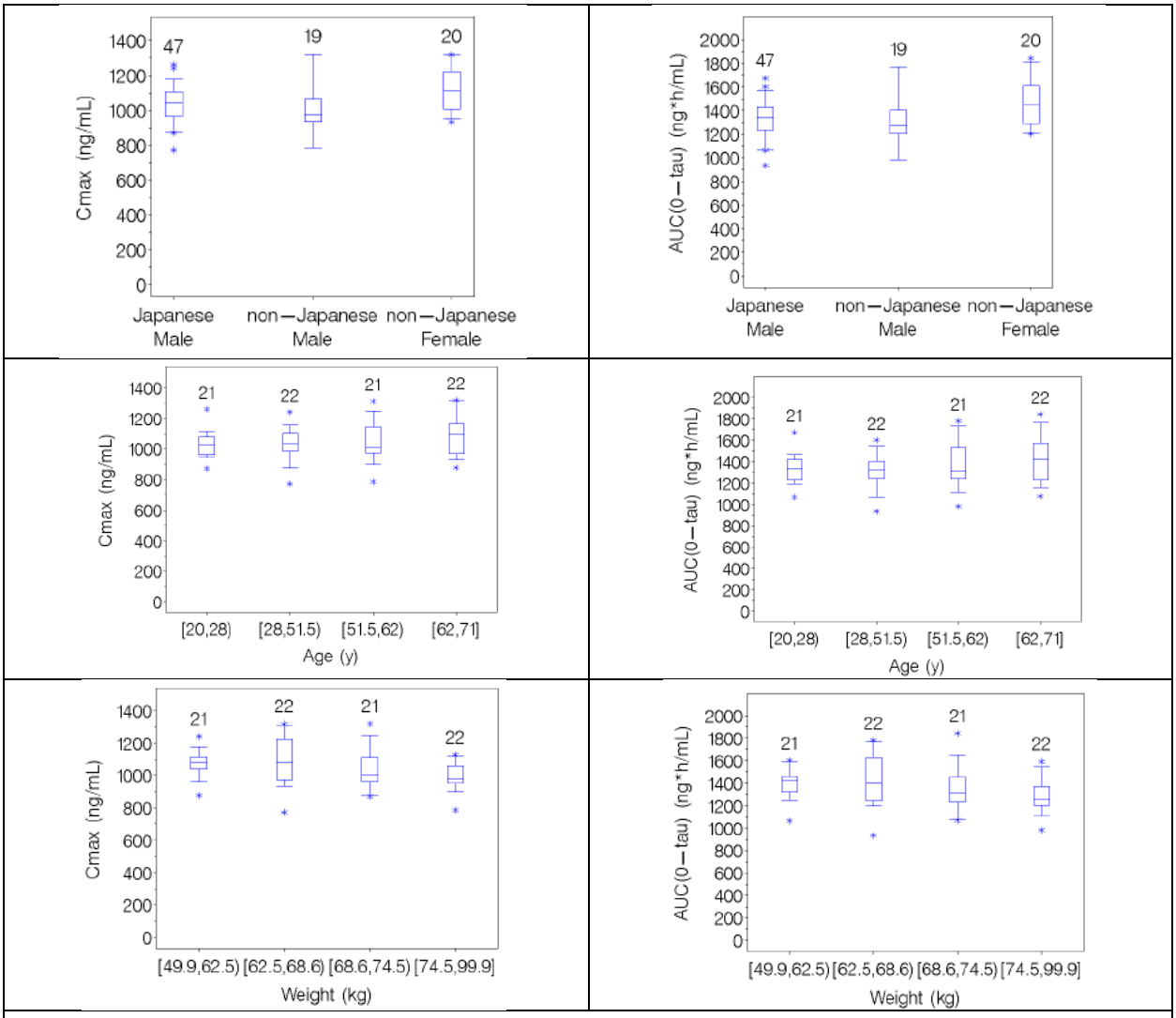
Figure 12. Observed, Population-predicted, and Individual-predicted MCI-186 (Edaravone) Concentration Versus Time Since Start of Infusion Plots of a Randomly Selected Subset of Subjects for the MCI-186 Final Population Pharmacokinetic Model.



Source : Figure 21 on page 140 in study report.

Since the model included nonlinear elimination, the exposure measurements calculated from the final analysis dataset could not be compared because Japanese and non-Japanese (US/EU) subjects did not receive the same dose. So for this assessment, using the individual Bayesian parameters from the final population PK model, a hypothetical dose of 60 mg MCI-186 infused over 1 hour daily for 14 days was administered to each subject in the final analysis dataset and exposures were calculated using numeric integration following the first and last dose. Boxplots of the exposures (C_{max} and $AUC_{0\text{-}tau}$) versus race, sex, and quartiles of age and weight are shown for the first and last dose in **Figure 13**.

Figure 13. Boxplots of Model-predicted Edaravone Exposures Versus Covariates Following a Single Hypothetical Dose of 60 mg/man Infused Over 1 Hour for All Subjects in the Final Analysis Dataset



Source : Figures 29 on page 150-155 in study report.

Figure 13 shows that the C_{max} and AUC0-tau model-predicted exposure measures did not exhibit any relationship to age and weight (all categories within 10% of lowest quartile) or race and sex (all within 10% of Japanese males).

Simulations to compare pharmacokinetics between Japanese and non-Japanese population

Demographic characteristics of sex, age, and weight for ALS patients were defined to allow the generation of an appropriate virtual ALS patient population. For Japanese ALS patients, data were available from MCI-186 clinical studies and the summary statistics of age and weight were calculated by sex and overall. For non-Japanese (US/EU) ALS patients, data were gathered from literature articles and only overall summary statistics of age and weight were available.

The virtual ALS patient populations, including 1,000 patients for each race, were generated as follows:
Japanese (n = 1,000)

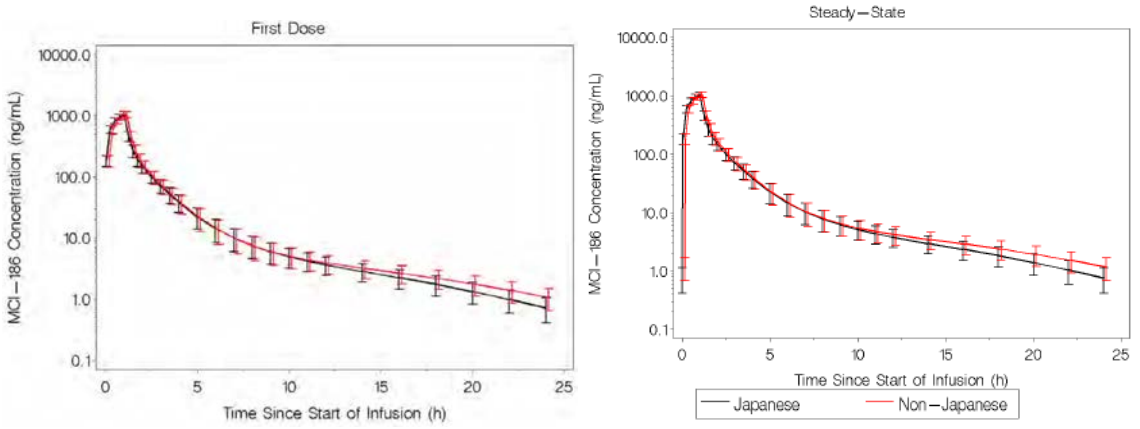
- 62% male
- Weight = 57.9 + 10.69•random normal(0,1) restricted to a range of 35 to 109 kg
- Age: 59 + 9.9•random normal(0,1) restricted to a range of 28 to 75 years

Non-Japanese (n = 1,000)

- 59% male
- Weight: 77.5 + 15.5•random normal(0,1) restricted to a range of 39 to 116 kg
- Age: 56 + 11.7•random normal(0,1) restricted to a range of 20 to 79 years

Three dosing regimens were selected for simulation:
30 mg, 60 mg (proposed dose for patients with ALS), and 120 mg infused over 1 hour daily for 14 days.
The mean (SD) plots of the concentration-time profiles displayed on a linear and log-linear scale stratified by day of dosing and race are shown in **Figure 14**. As expected, based upon the significant covariates in the model and the relationship between exposures and model parameters, the concentration-time profiles for the 2 races are similar except for the final phases of decline as the curve approaches C_{tau}.

Figure 14. Mean and Standard Deviation Plot of Simulated MCI-186 (Edaravone) Concentration Versus Time Since Start of Infusion in Amyotrophic Lateral Sclerosis Patients Stratified by Dosing Day and Race for a Dose of 60 mg/man Infused Over 1 Hour (Displayed on a Log-Linear Scale)



Source : Figure 42 on page 167 in sponsor report.

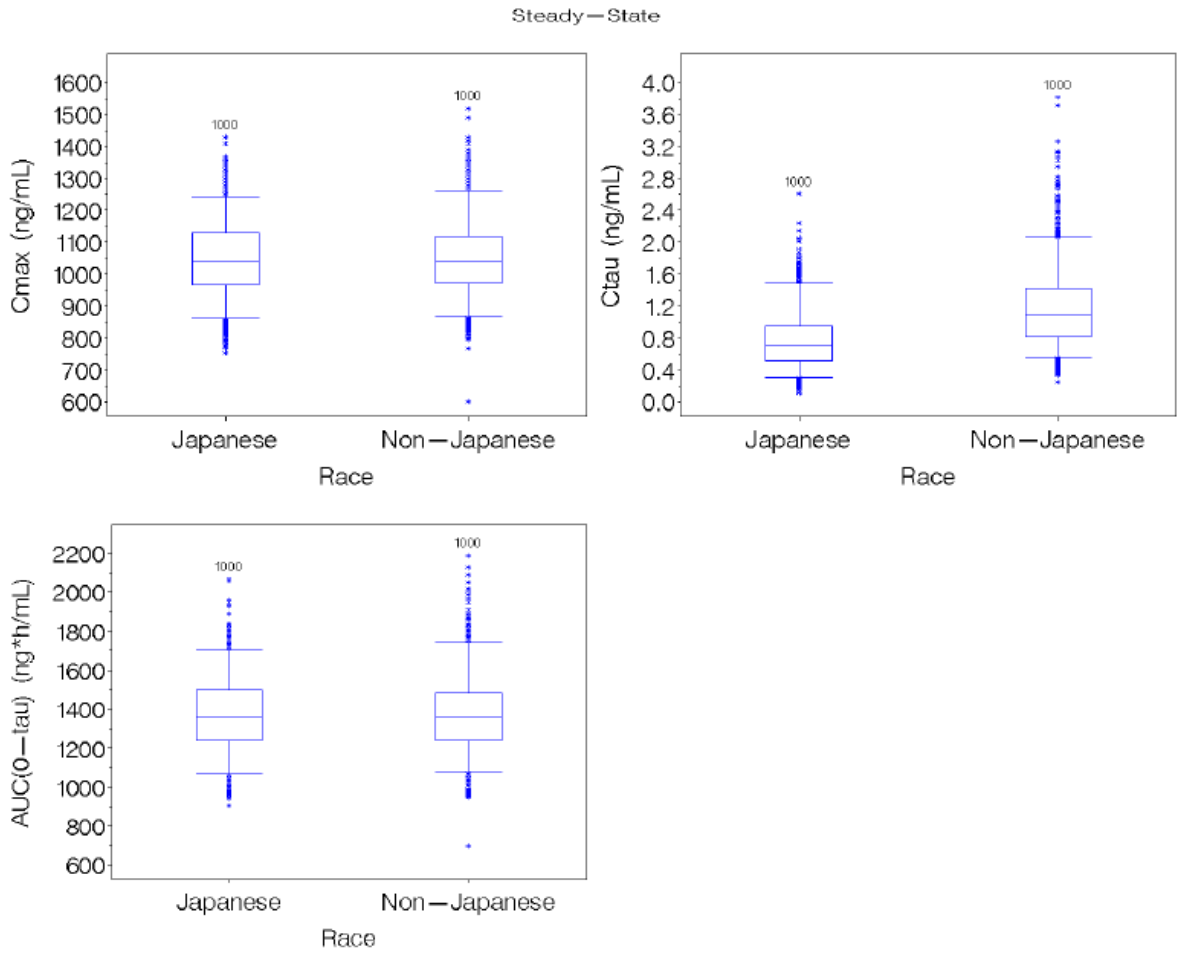
Table 20. Simulation Results from Population Pharmacokinetic Analyses for 60 mg/60 min, Once Daily for 14 Days (Simulation for Virtual 1000 Patients per Subpopulation)

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: Summary of clinical pharmacology, page 65, originally from popPK report 002525)

Boxplots of simulated MCI-186 exposures in ALS patients versus race for 60 mg infused over 1 hour is shown in **Figure 15**. The boxplots also show that the exposures are similar for the 2 populations after 60 mg dose. These findings support same dosing guidelines in Japanese and non-Japanese (Caucasian) ALS patients.

Figure 15. Boxplots of Simulated MCI-186 (Edaravone) Exposures in Amyotrophic Lateral Sclerosis Patients Versus Race: 14 Daily Doses of 60 mg/man Infused Over 1 Hour

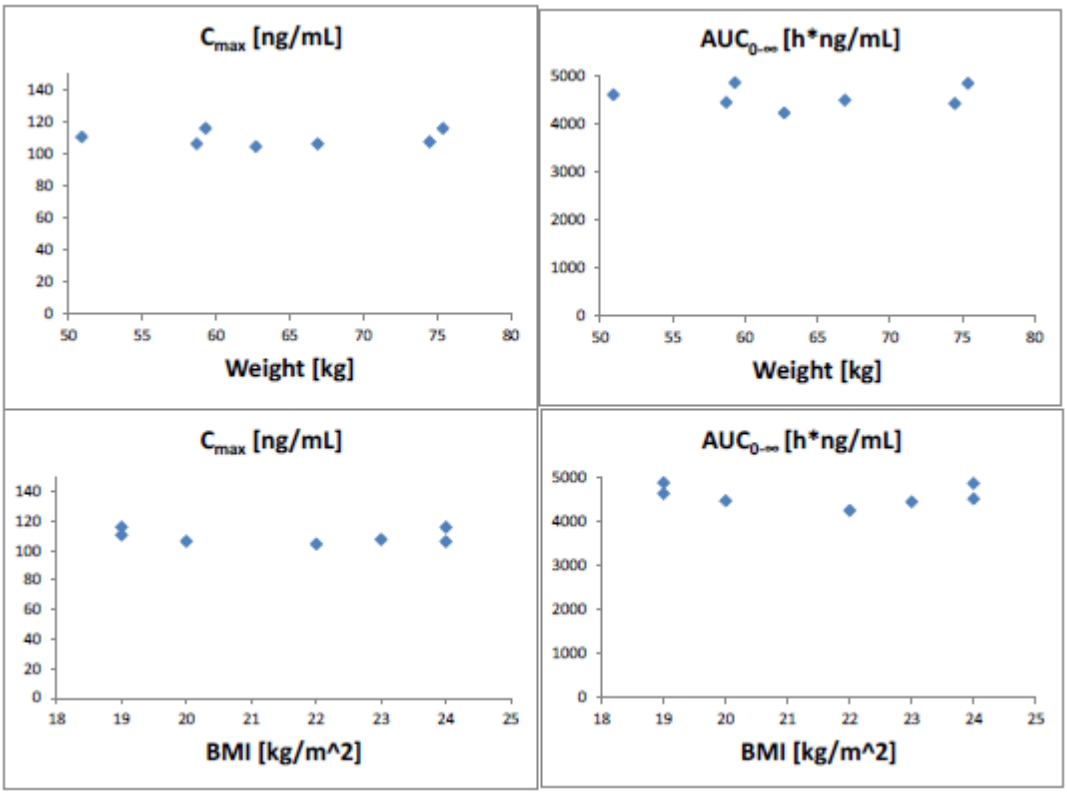


Source : Figure 35 on page 160 in sponsor report.

Reviewer's Comments: The population pharmacokinetic analysis conducted by the sponsor is reasonable. Various model diagnostics support the structural model. The analysis conducted by the sponsor shows that edaravone plasma concentrations will be similar between Japanese and non-Japanese patients due to the lack of race and body effect on apparent clearance of edaravone. The reviewer considered other sources of information that support these findings. To note

- *The relationships between body weight or body mass index (BMI) and PK parameters (C_{max} or AUC) were investigated in Study MCI186-14 where a fixed dose of 240 mg edaravone was administered.* **Figure 16** *shows that the observed edaravone concentrations are similar across body weight groups.*

Figure 16. Relationship between Body Weight/Body Mass Index and Pharmacokinetic Parameters (120 mg/Subject/24 hr for 2 Days) in Japanese Healthy Male Adults.



Source : Figure 2.7.2.3.3-3 on page 67 in sponsor report.

Figure 16 *shows that even if slight average body weight differences (57.9 vs 77.5 kg) between Japanese and non-Japanese populations are considered, the metrics related to exposure of edaravone (C_{max}, $AUC_{0-\infty}$) should be similar between the two groups.*

- *In addition, the similarity in proportion of metabolites (glucuronide and sulfate conjugate) excreted in urine supports the lack of race effect on the apparent clearance of edaravone in the population pharmacokinetic model.*

Overall, the conclusions that plasma levels of edaravone will be similar in Japanese and non-Japanese patients are acceptable.

Reviewer's Analysis

Aim
To verify population pharmacokinetic analyses that show non-Japanese ALS patients (Caucasian ALS patients as analyzed by sponsor) can be administered the same dosing regimen of edaravone as studied in Japanese ALS patients.

Data
The dataset (poolpk.nmdat) submitted by the sponsor were used for the analysis.

Software
NONMEM® Version 7.3 was used for the analysis.

Analysis Strategy

- Execute the base and final population PK model to verify sponsor reported pharmacokinetic parameters.
- Analyze other sources of information that support findings from population PK analysis.

Findings
The reviewer was able to confirm sponsor's reported PK parameters from the base model and final model. For additional information on the acceptability of popPK model and conclusions that RACE (Japanese versus non-Japanese) does not significantly influence the pharmacokinetics of edaravone, please refer to "Reviewer's Comments" after **Figure** 15. Overall, the results show that dose/dosing regimen of edaravone can be similar between studied Japanese ALS patients and unstudied non-Japanese ALS patients.

4.4 In Vitro Assessment of Drug Interaction Potential

1. Edaravone as a substrate drug

Metabolic interaction: Edaravone is metabolized mainly by sulfotransferases and to a lesser extent by UGTs, as sulfate metabolite is the predominant moiety in systemic circulation. *In vitro* experiments suggested that liver has much higher sulfotransferase activity than kidney (Tables 12 and 21).

Table 21. UGT, sulphotransferase (ST), β-glucuronidase (β-G) and sulfatase (S) activities in liver S9 of rat, dog and human

Species	Activity (pmol/min/mg protein)			
	UGT	ST	βG	S
Rat (n=3)	59 ± 2.6	1917 ± 20	42 ± 4.5	17 ± 8.8
Dog (n=3)	184 ± 13	1186 ± 57	26 ± 8.5	22 ± 6.9
Human (Mixture, n=1)	81	226	4.7	163

(Source: report for study s-29, page 16)

In vitro experiments using microsomes expressing human UGTs suggested that multiple UGTs were responsible for the formation of glucuronide conjugate, mainly UGT1A9, 2B17, 1A6, 2B7. Furosemide or salicylic acid, two drugs also undergoing glucuronidation, did not inhibit glucuronidation of edaravone in liver and kidney microsomes at concentrations 10 times of their C_{max} in humans. The study also

demonstrated that metoclopramide or acetaminophen, which is subject to sulfation, did not inhibit the formation of edaravone sulfate conjugate in human liver sf9 fractions at concentrations up to 10 times of their C_{max} in humans. Overall, edaravone is less subject to the impact of inhibitors or inducers of CYP enzymes, or inhibitors of UGTs or sulfotransferases.

Transporter: Edaravone (100 μM) had a high permeability (32.0×10^{-6} cm/sec) across Caco-2 cells monolayer, and was a weak substrate of OAT1 and OAT3 (uptake of edaravone by OAT1- and OAT3-expressing HEK293 cells was just twice the uptake by the vector transfectant). Since the permeability of edaravone is high, the contribution of transporters to its transport across cell membranes is limited. Thus, the PK of edaravone is unlikely to be affected by inhibitors of major transporters.

Protein binding: The protein binding of edaravone to human serum protein was 91-92% and independent on concentrations (0.1 – 50 μM) as measured by equilibrium dialysis. The binding of edaravone with human serum albumin ranged from 80.7 to 95.4 % and its binding with α-1-acid glycoprotein was between 10.3 and 16.3 %. The human serum protein binding of edaravone, the sulfate, and glucuronide conjugate measured by ultrafiltration was 92.0 – 92.8%, 99.3%, and 35.5-38.9%, respectively. Protein binding of edaravone was not affected by warfarin, salicylic acid, ticlopidine, nizofenone, riluzole, tocopherol nicotinate, or tocopherol, suggesting that the potential of drug interaction due to protein binding replacement is low.

2. Edaravone as an inhibitor drug

Metabolic interaction: Using human liver microsomes, the IC_{50} of edaravone, its sulfate and glucuronide conjugates for CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, UGT1A1, and UGT2B7 was above 100 μM, except that edaravone inhibited CYP2C9 with an IC_{50} of 84.5 μM. It was found that edaravone was a time-dependent inhibitor of CYP2C9 with k_{inact} and K_I values being 0.0111 min^{-1} and 215 μM, respectively. Using a mechanistic static model described in the DDI Guidance, the AUCR is calculated as 1.08 (C_{max} of edaravone at steady state is around 6 μM, free fraction in plasma is 0.08), which is less than the cut-off value of 1.25, suggesting that the potential of edaravone inhibiting CYP2C9 *in vivo* is low. Thus, at therapeutic dose, edaravone and its metabolites are not anticipated to inhibit these major CYP enzymes and UGT1A1 or 2B7.

Edaravone was found to inhibit glucuronidation of furosemide in human kidney microsomes with an IC_{50} of 21.8 μM, but not in human liver microsome preparations. The IC_{50} value far exceeds the unbound C_{max} of edaravone (0.48 μM). In addition, a significant amount of furosemide dose is excreted into urine as unchanged drug. Therefore, edaravone is unlikely to cause clinically significant DDI by inhibiting glucuronidation metabolism of furosemide.

Transporter: Edaravone and its metabolites were tested as inhibitors for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2. Inhibitory effects were only observed for edaravone towards BCRP and OAT3 with IC_{50} of 121 μM and 72.3 μM, respectively, and for edaravone sulfate conjugate against OAT1 and OAT3 with IC_{50} of 13.6 μM and 2.74 μM, respectively. The $C_{max,ss}$/ IC_{50} ratio of edaravone for BCRP is 0.05, less than a cut-off value of 0.1. The unbound $C_{max,ss}$/ IC_{50} ratio of edaravone for OAT3 or edaravone sulfate conjugate for OAT1 is also below 0.1. The unbound $C_{max,ss}$/ IC_{50} ratio of sulfate conjugate for OTA3 is 0.11 (C_{max} of the sulfate metabolite was about 5 folds of that of parent drug, i.e., 31 μM. fu,p of the metabolite is 0.01), just marginally above the cut-off value of 0.1. Thus, it is concluded that edaravone and its metabolites are not expected to inhibit these major transporters *in vivo*.

Protein binding: Edaravone (10 μg/mL, i.e., 57.4 μM) did not alter the plasma protein binding of warfarin and salicylic acid.

3. Edaravone as an inducer

Effects of edaravone, its sulfate and glucuronide metabolites on mRNA expression of CYP1A2, 2B6, or CYP3A4 were examined after treatment with primary hepatocytes for 2 days. Induction effects were seen for edaravone and its sulfate conjugate, in the order of CYP1A2 > CYP3A4 > CYP2B6. Since the sulfate conjugate had a quite low permeability across Caco-2 cell monolayers (comparable to mannitol, a paracellular marker), its induction effects were considered due to edaravone which was generated from degradation of the sulfate conjugate in medium during incubation. Edaravone induced CYP2B6 or CYP3A4 mRNA expression or enzyme activity to > 2 fold of the control group only at concentrations of 100 µM or higher, which was well above its C_{max}.

In one experiment (Study B150749), edaravone induced CYP1A2 expression (≥ 2-fold of the control group) at 3 µM and higher concentrations. Yet, in another study (15F3731), induction of CYP1A2 mRNA and enzyme activity was observed only for edaravone concentrations of 30 µM and higher. This may be due to higher sensitivity of the hepatocytes used in Study B150749 to induction effect, since the response to omeprazole, the positive control, was much higher than that seen in Study 15F3731. In fact, the induction effect of edaravone at 30 µM on CYP1A2 mRNA expression was just 20% of the response of the positive control in Study B150749.

Nevertheless, based on the data from Study B150749, the values for the half-maximal effective concentration (EC_{50}) and maximum induction effect (E_{max}) of edaravone for CYP1A2 was calculated as 26.2 to 67.6 µM and 10.6 to 82.1, respectively. In comparison, The EC_{50} of omeprazole was 36.7 to 59.7 µM, and the E_{max} was 387 to 505. Using a mechanistic static model described in the DDI Guidance, an *in vitro-in vivo* scaling factor (d) for induction was estimated based on the EC_{50} and E_{max} of omeprazole and *in vivo* interaction between omeprazole and caffeine, a CYP1A2 substrate. The estimated d value was then used along with the EC_{50} and E_{max} of edaravone to derive an estimation of the AUCR of riluzole when co-administered with edaravone. Riluzole is mainly metabolized by CYP1A2 and is commonly used to treat ALS. The AUCR of riluzole (the ratio of riluzole AUC in the presence of edaravone divided by its AUC in the absence of edaravone) was predicted to be 0.98, 0.99, and 0.86, respectively, suggesting that edaravone may not significantly decrease riluzole concentrations. It should also be noted that most of the patients in the Phase 3 trials of edaravone were on riluzole treatment. Thus, even if there was an induction effect of edaravone on CYP1A2 *in vivo* and thus may reduce riluzole concentrations, such interaction is not expected to impair the efficacy of riluzole plus edaravone treatment.

Overall, at therapeutic dose, edaravone is not expected to significantly induce CYP1A2, 2B6, or 3A4/5 in humans, either.

4.5 Enrichment, Stratification, and/or Biomarker-based Assessment

Enrichment strategy was adopted in the pivotal Phase 3 trial (MCI186-19).

Table 22. Phase 2 and Phase 3 Studies in Japanese Patients with Amyotrophic Lateral Sclerosis

Phase / Study number	Description	Study type	Number of subjects in FAS (active)	Treatment regimen	Primary/ main endpoint	Results
Phase II						
MCI186-12	Exploratory study	OL	19 (19)	30 and 60 mg[b]	ALSFRS-R suppression rate (Baseline to Cycle 6)	Table 2.7.3-5, Module 2.7.3
Phase III						
MCI186-16	Confirmatory study in ALS grade 1 and 2	DB PC	205 (101)	Placebo or 60 mg[b]	ALSFRS-R score (Baseline to Cycle 6) (For MCI186-17, Cycle 7 to Cycle 12)	Table 2.5.4-1
MCI186-17	Extension study of MCI186-16	DB PC	180 (136)			Table 2.5.4-2
MCI186-18	Exploratory study in ALS grade 3	DB PC	25 (13)			Table 2.5.4-4
MCI186-19	Pivotal replication of confirmatory study in ALS grade 1 and 2[a] [and extension study]	DB PC [OL]	137 (69) [(123)]			Table 2.5.4-5

[a] Inclusion criteria in Study MCI186-19 were further refined using ALSFRS-R, %FVC, etc. as described in this section.
[b] Cycle 1: IV administration of the study drug once each day for 14 consecutive days, followed by a 2-week drug-free period. Cycle 2 and thereafter: IV administration of the study drug once a day for any 10 days within 2-week period, followed by a 2-week drug-free period.

(Source: Clinical Overview, page 13)

Subjects with Japan ALS severity grade 1 or 2 were randomized to edaravone (n = 101) or placebo (n = 104) and evaluated using ALSFRS-R in Study MCI186-16. While a beneficial trend favoring edaravone was observed in the full analysis set, the primary endpoint did not reach statistical significance. With additional exploratory analyses, the Sponsor found that the beneficial trend was mainly driven by subjects who had functionality retained in most ADL domains with normal respiratory function, named as Efficacy Expected Subpopulation (EESP). The EESP was defined as subjects with

- Each individual item of the ALSFRS-R of 2 or better at Baseline (i.e., Functionality retained in most ADL domains)
- A percent forced vital capacity (%FVC) of 80% or greater at Baseline (i.e., Normal respiratory function).

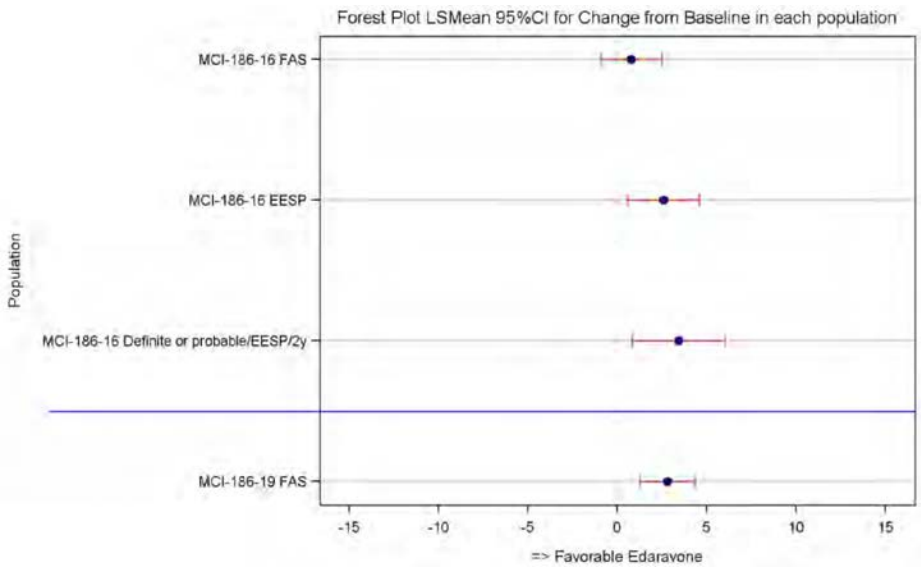
As further analysis, stable subjects unlikely to have significant disease progression during the study period (24 weeks) were excluded. In addition to the EESP criteria, subjects meeting the following two criteria were defined as 'Definite or Probable/EESP/2y'.

- Definite or Probable ALS diagnosis based on the El Escorial and revised Airlie House diagnostic criteria at preregistration (To ensure diagnosis of ALS)
- Within 2 years of initial ALS symptom onset at preregistration (To exclude subjects who were stable for long term with ALS).

Study MCI186-17 was a combined extension and randomized placebo-controlled study with subjects continuing from Study MCI186-16. Subjects who received edaravone in Study MCI186-16 were reassigned to edaravone or placebo. Subjects who received placebo in Study MCI186-16 were switched to edaravone. While a beneficial trend favoring edaravone based on ALSFRS-R score was observed in the full analysis set, the difference from placebo was not statistically significant. However, both the EESP and the Definite or Probable/EESP/2y population showed beneficial trends similar to those observed in Study MCI186-16 in favor of edaravone while not reaching statistical significance. The Sponsor considered that this may be due to the limited number of subjects.

To confirm these findings, Study MCI186-19 was conducted and *prospectively* designed as a trial in the 'Definite or Probable/EESP/2y' population. This study was considered as the pivotal trial. The primary endpoint of ALSFRS-R score showed a statistical significance favoring edaravone at the end of Cycle 6 (24 weeks).

Figure 17. Forest Plot of ALSFRS-R between Baseline in Cycle 1 and the End of Cycle 6 (MMRM analysis) for Studies MCI186-16 (FAS, EESP, Definite or Probable/EESP/2y) and MCI186-19 FAS



(Source: Clinical Overview, page 37)

The safety and efficacy findings from these studies are considered applicable to all ALS patients. Please refer the review of Medical Officer, Dr. Christopher Breder, for more details.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XINNING YANG
01/25/2017

VENKATESH A BHATTARAM
01/25/2017

KEVIN M KRUDYS
01/25/2017

SREEDHARAN N SABARINATH
01/25/2017

MEHUL U MEHTA
01/25/2017