CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 215446
Link to EDR	\\CDSESUB1\evsprod\NDA215446\0001
Submission Date	November 12, 2021
Submission Type	505(b)(1) pathway with Priority Review
Brand Name	RADICAVA ORS
Generic Name	Edaravone Oral Suspension
Dosage Form and Strength	Oral Suspension (105 mg/ 5 mg/mL)
Route of Administration	Oral
Proposed Indication	Amyotrophic lateral sclerosis (ALS)
Applicant	Mitsubishi Tanabe Pharma Corporation
Associated IND	IND 138145
OCP Review Team	Ramakrishna Samala, Ph.D. Bilal AbuAsal, Ph.D.
OCP Final Signatory	Bilal AbuAsal, Ph.D. (Team Leader)

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1. Executive Summary

In this original New Drug Application (NDA), the Applicant, Mitsubishi Tanabe Pharma Corporation, is seeking approval for RADICAVA ORS (edaravone oral suspension) via 505(b)(1) pathway for the treatment of Amyotrophic Lateral Sclerosis (ALS) in adults.

The applicant is seeking approval for RADICAVA ORS based on the PK bridging of the proposed RADICAVA ORS oral suspension to the reference RADICAVA intravenous injection, that was approved by the FDA in 2017. The proposed dosing frequency of the RADICAVA ORS is the same as that of the reference product.

The submission included: 1) a pivotal relative bioavailability (BA) study (Study MT-1186-J03) to evaluate single-dose bioequivalence of 105 mg oral suspension to 60 mg IV formulation of edaravone in the fasting state in healthy adult subjects, 2) a Phase 3 study (MT-1186-A01) in ALS patients to evaluate the safety/tolerability of RADICAVA ORS, 3) a Phase 1 study (MT-1186-J02) to evaluate DDIs, and effect of food and race on the PK of oral edaravone, 4) a Food Effect (FE) study to evaluate the effects of various fed conditions on the PK of edaravone when administered as an oral suspension 105 mg (Study MT-1186-J06), 5) a comparative bioavailability study of edaravone when administered orally and via nasogastric tube (Study MT-1186-Z-101), and 6) a Phase 1 study to evaluate single ascending doses, multiple ascending doses, food effect and effect of race (MT-1187-J01).

The primary focus of this review is to evaluate the bioequivalence between edaravone 60 mg over 60 min IV infusion and edaravone oral suspension 105 mg, effect of timing and type of food consumption on edaravone pharmacokinetics, need for dose adjustment due to the extrinsic factors, specifically, concomitant administration of edaravone oral suspension with the substrates of CYP3A4, BCRP or OAT3, and effect of edaravone administration via PEG/NG tube on the edaravone pharmacokinetics

Results from the pivotal BE study demonstrated that geometric LS mean ratios (GMR) of plasma exposures of edaravone after oral and intravenous administration met the bioequivalence criteria for AUC (GMR PO/IV is 0.977 and 90% CI is 0.917 -1.041) but not for C_{max} (GMR PO/IV is 1.217 and 90% CI is 1.090-1.359). However, both sulfate and glucuronide exposures (C_{max} and AUC) after oral administration were >1.3-fold greater than those after intravenous administration. There were no safety issues associated with increase in edaravone C_{max} and increase in metabolites exposures and the dose has been well tolerated without serious adverse events according to the 24-week interim analysis of the ongoing open label safety study (MT-1186-A01). At the 24-week interim analysis, 185 subjects have been enrolled and 160 (86.5%) of them completed 24-week study period. Dosing administration with regards to food was updated based on results from the food effect studies. No significant clinical drug interactions were observed between edaravone and substrates of CYP3A4, BCRP or OAT3, hence, no dose

adjustment recommended for concomitant administration of edaravone oral suspension and substrates of CYP3A4, BCRP or OAT3.

The office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspection for the pivotal relative bioavailability study, MT-1186-J03[1]. The OSIS have conducted a remote review of the analytical portion of the study and observed changes in peak integration parameters after obtaining results from the initial integration. However, the OSIS audit report concluded that the changes in peak integration parameters had no impact on the integrity of the data and the audited data are reliable.[2]

2. Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under NDA215446 and recommends approval of RADICAVA ORS for the treatment of Amyotrophic Lateral Sclerosis. The review team determined that no post-market commitment or post-market requirement is needed.

Labeling recommendations

1. RADICAVA ORS can be administered by mouth or via feeding tube.
2. RADICAVA ORS should be taken in the morning on an empty stomach after overnight fasting and recommended not to consume food for 1 hour after each dose. If it can't be administered after overnight fasting, patients should wait for 2, 4 and 8 hours after consuming a caloric supplement, low-fat meal, and high-fat meal, respectively.
3. Patients switching from RADICAVA to RADICAVA ORS can be switched using same dosing frequency. However, patients should consider timing with regards to the type of food consumed.
4. Both sulfate and glucuronide metabolite exposures were (b) (4)-fold greater after RADICAVA ORS oral administration than those after RADICAVA intravenous infusion.

3. Background and Regulatory History

RADICAVA, edaravone 30 mg /100 mL injection, for the treatment of Amyotrophic Lateral Sclerosis was approved by the United States Food and Drug Administration in 2017 under New Drug Application 209176. The recommended dose during the initial treatment cycle is 60 mg intravenous infusion over 60 minutes daily for 14 days followed by a 14-day drug free period. In the subsequent cycles, 60 mg intravenous infusion over 60 minutes for 10

[1] OSIS Bioequivalence Audit Consult Request in DARRTS dated January 19, 2022

[2] Bioequivalence Establishment Inspection Report Review in DARRTS dated April 4, 2022

days out of 14-day periods, followed by 14-day drug-free periods. However, long-term, frequent IV infusions of RADICAVA are a highly significant burden for patients with a terminal illness, and for the caretakers and healthcare professionals who help prepare and deliver those infusions to them. With a goal of reducing the burden, the applicant has developed an oral suspension that result in similar plasma edaravone exposures and safety profiles as that of RADICAVA.

The clinical development program included: six phase 1 studies evaluating the drug-interaction potential, effect of race, effect of PEG tube, and the effect of food, a pivotal BE study (MT-1186-J03), and a Phase 3 study (MT-1186-A01) in ALS patients evaluating the safety/tolerability of RADICAVA ORS have been reviewed and summarized under sections 5 and 6. Study numbers with the study titles and a brief description are provided in Table 1.

Table 1. Clinical studies included in the NDA215446 application package

Study #	Study Title	Brief Description
MT-1186-J01	Phase I Study of Oral Edaravone in Healthy Adult Males (Single- and Multiple-dose Study)	SAD and MAD study
MT-1186-J02	Clinical Pharmacology Study of Oral Edaravone in Healthy Adult Males (Drug Interaction Study and Preliminary Regimen-Finding Study)	Regimen finding study DDIs study
MT-1186-J03	Bioequivalence Study of Oral Suspension and Intravenous Formulation of Edaravone in Healthy Adult Subjects	Pivotal BE study
MT-1186-J06	Clinical Pharmacology Study of Oral Edaravone in Healthy Adult Subjects (Food	Food effect
MT-1186-Z-101	A Phase I, Randomized, Open-Label, Crossover-Design, Single-Dose Study to Investigate the Safety, Tolerability and Comparative Bioavailability of Oral Edaravone Administered orally and via a Nasogastric Tube (NGT) in Healthy Adult Subjects	Effect of NGT
MT-1186-J04	Clinical Pharmacology Study of Oral Edaravone in Patients with Amyotrophic Lateral Sclerosis (ALS)	Effect of PEG tube/NGT

MT-1186-J05	Clinical Pharmacology Study of Oral Edaravone in Amyotrophic Lateral Sclerosis (ALS) Patients with Percutaneous Endoscopic Gastrostomy (PEG)	Effect of PEG tube/NGT
MT-1186-A01	A Phase 3, Multi-Center, Open-Label, Safety Study of Oral Edaravone Administered over 48 Weeks in Subjects with Amyotrophic Lateral Sclerosis (ALS)	24-week interim analysis submitted

Source: Summary of Clinical Pharmacology Studies[3]

4. Clinical Pharmacology Highlights of Edaravone Oral Suspension

The clinical pharmacology program assessed the PK, effect of type of food and timing on the PK, and DDI of edaravone in a series of *in-vitro* and clinical studies. The clinical pharmacology highlights are summarized below.

Absorption

Edaravone oral suspension is to be administered on empty stomach after overnight fasting and do not eat or drink for 1 hour. Following its oral administration, peak plasma concentrations (T_{max}) reached within one hour with a bioavailability of 57%. More than dose proportional increase in C_{max} and AUC_{0-24h} was observed between 30 - 300 mg oral doses.

Distribution

Edaravone has a serum protein binding of > 92% and its volume of distribution is 63.1 L.

Elimination

Terminal elimination half-life of unchanged edaravone after oral administration is 4.5 - 9.75 hours.

Metabolism

Edaravone has two metabolites, edaravone sulfate and edaravone glucuronide. Prominent plasma conjugate is edaravone sulfate, and its formation is mediated by sulfotransferases. Prominent urine conjugate is edaravone glucuronide, and its formation is mediated by UGT1A1, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B17. Following RADICAVA ORS (edaravone 105 mg) oral administration,

[3] \\CDSESUB1\evsprod\nda215446\0001\m2\27-clin-sum\summary-clin-pharm.pdf

edaravone metabolite exposures are 1.3 to 2.2-fold higher than those after RADICAVA (edaravone 60 mg/60 min IV).

Excretion

Edaravone and its metabolites are excreted in urine. More than 80% of the administered dose is recovered in urine, of which, 70-90% is glucuronide conjugate, 6-8% is sulfate conjugate, and < 1% is unchanged edaravone. The effect of renal and hepatic impairment is not expected to be significantly different from RADICAVA injection.

5. Summary of Pivotal Relative Bioavailability Study (MT-1186-J03)

The applicant has conducted a pharmacokinetic study to demonstrate the bioequivalence of edaravone oral suspension 105 mg to edaravone 60 mg/60 minute intravenous infusion.

Title

Bioequivalence Study of Oral Suspension and Intravenous Formulation of Edaravone in Healthy Adult Subjects

Primary Objective

To evaluate the single-dose bioequivalence of oral suspension and IV formulation of edaravone in the fasting state in healthy adult subjects.

Study Population

Healthy Japanese adult male or female volunteers aged between 20 and 45 years at the time of informed consent were enrolled in the study.

Study Design

Forty-two subjects were randomly allocated to 2 groups of 21 subjects. It was carried out by a 2-period, 2-sequence, crossover, randomized, open-label study. The duration of hospitalization was 7 days and 6 nights. Study design and treatment periods are provided in **Table 2** and **Figure 1.**

Table 2. Study design and Treatment periods for the pivotal BE study MT-1186-J03

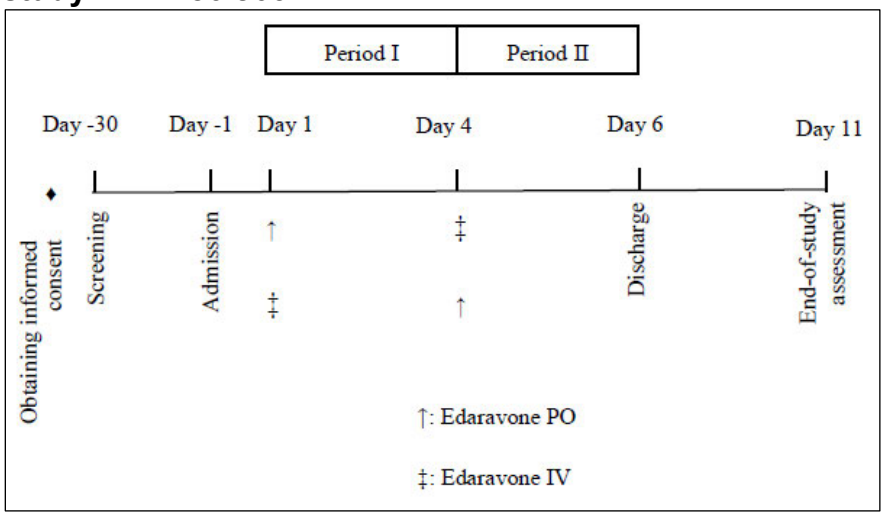
Subjects	Period I	Period II
Advance administration of edaravone oral suspension group (PO - IV; 21 subjects)	Edaravone oral suspension 105 mg	Edaravone IV formulation 60 mg/60 min
Advance administration of edaravone IV formulation group (IV - PO; 21 subjects)	Edaravone IV formulation 60 mg/60 min	Edaravone oral suspension 105 mg

Source: MT-1186-J03 study report, page 20

Selection of Doses

RADICAVA 60 mg over 60 minutes IV infusion was approved for ALS in 2017. It was considered as reference in this study. Clinical studies MCI-186-J25, MT1186-J01, and MT-1186-J02 estimated that edaravone oral suspension 105 mg would provide corresponding pharmacokinetic exposures to those provided by 60-minute IV infusion of edaravone 60 mg.

Figure 1. Timelines for screening and treatment administrations in the pivotal BE study MT-1186-J03



Source: MIT-1186-J03 study report, page 27

PK Sampling

Multiple blood samples were collected up to 48 hours for the quantification of edaravone, edaravone sulfate and edaravone glucuronide from the subjects who were assigned to edaravone oral suspension. A total of 16 blood samples were collected in Period I at the following time points Predose, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, and 48 hours. A total of 17 blood samples were collected in Period II at the following time points Predose, 0.25, 0.5, 1, 1.083, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours.

Multiple blood samples were collected up to 48 hours for the quantification of edaravone, edaravone sulfate, and edaravone glucuronide from the subjects who were assigned to edaravone IV formulation group. A total of 17 blood samples were collected in Period I at the following time points Predose, 0.25, 0.5, 1, 1.083, 1.25, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, and 48 hours. A total of 17 samples were collected in Period II at the following time points Predose, 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, and 48 hours.

PK Analysis Method

Validated LC-MS/MS based bioanalytical methods were used to quantify plasma concentrations of unchanged edaravone, edaravone sulfate and edaravone glucuronide. Method and its validation report for each compound was available in study report NB17011V.

Number of Subjects (Planned and Analyzed)

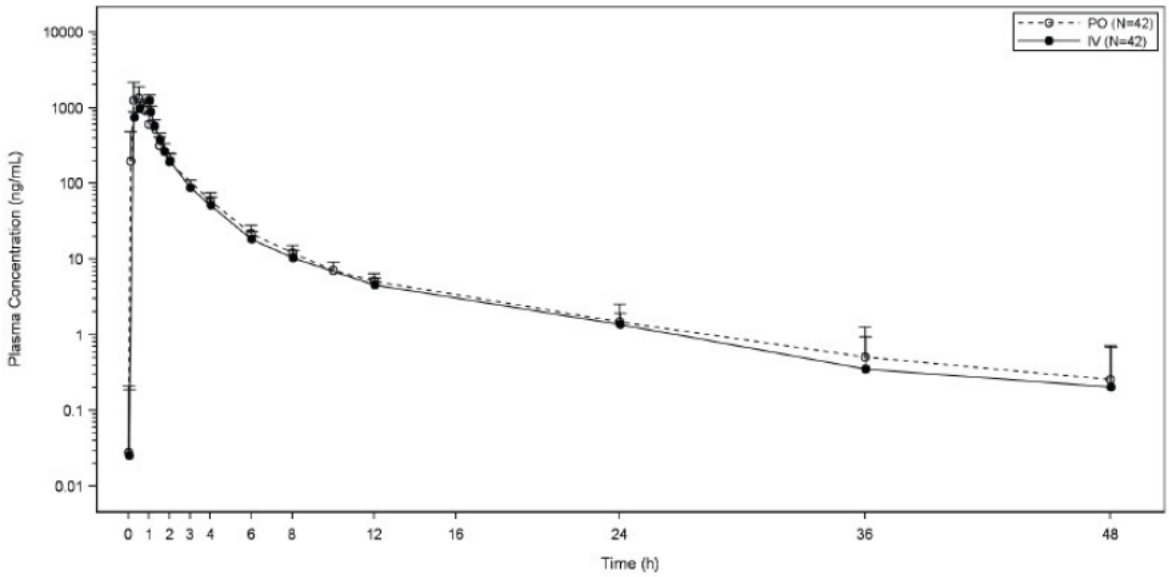
A total of 93 subjects gave informed consent and were screened. 50 subjects were eligible for the study, 43 subjects were not eligible because of the withdrawal of consent (9), meeting exclusion criteria (16) and other reasons (18). 42 subjects were randomly divided into two groups at 1:1 ratio. 8 subjects were in reserve. All 42 subjects successfully participated and completed both the treatment arms.

PK Results

Unchanged edaravone

The mean plasma concentration-time profiles of unchanged edaravone and plasma pharmacokinetics parameters after administration edaravone oral suspension 105 mg and edaravone 60 mg intravenous infusion are shown in **Figure 2** and **Table 3**, respectively.

Figure 2. Mean plasma concentration-time profile of unchanged edaravone after edaravone 105 mg oral suspension and 60 mg/60 minutes IV formulation administration



Source: MT-1186-J03 study report. Figure 11-2, page 60

Table 3. Plasma pharmacokinetic parameters of unchanged edaravone

Treatment	Plasma PK parameter	t_{max}[a] (h)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	F (%)
PO	Mean	0.50	1656	1743	1762	9.75	57.3
(N=42)	CV%	0.25, 0.75	44.3	30.7	30.6	86.9	21.9
IV	Mean	1.00	1253	1720	1736	8.82	-
(N=42)	CV%	0.98, 1.02	18.3	18.9	19.1	94.4	-

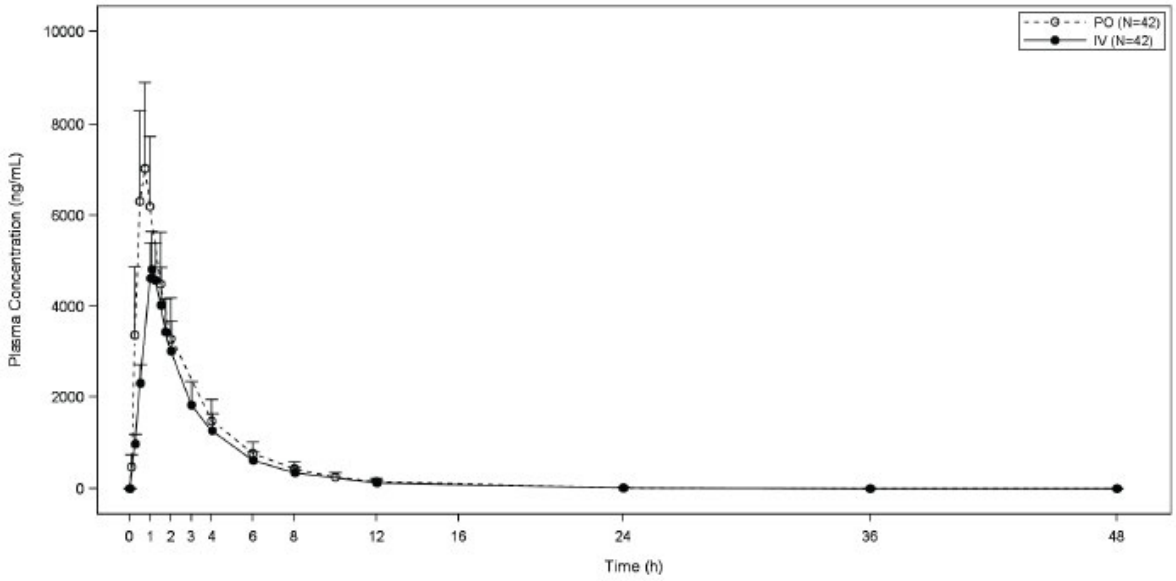
[a]: Median and range
CV: coefficient of variation

Source: MT-1186-J03 study report. Table 11-2, page 61

Edaravone Sulfate

The mean plasma concentration-time profiles and plasma pharmacokinetic parameters of edaravone sulfate after administration of edaravone 105 mg oral suspension and edaravone 60 mg/60 min intravenous infusion are shown in **Figure** 3 and **Table** 4, respectively.

Figure 3. Mean plasma concentration-time profiles of edaravone sulfate after administration of edaravone 105 mg oral suspension and edaravone 60 mg/60 minutes intravenous infusion



Source: MT-1186-J03 study report, Figure 11-3 (Top), page 64

Table 4. Plasma pharmacokinetic parameters of edaravone sulfate after administration of edaravone 105 mg oral suspension and edaravone 60 mg/60 minutes intravenous infusion

Treatment	Plasma PK parameter	t_{max}[a] (h)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
PO	Mean	0.75	7291	20031	20055	5.77
(N=42)	CV%	0.50, 1.00	26.0	26.2	26.2	32.1
IV	Mean	1.08	4843	15024	15055	7.58
(N=42)	CV%	0.98, 1.25	16.9	23.8	23.8	31.5

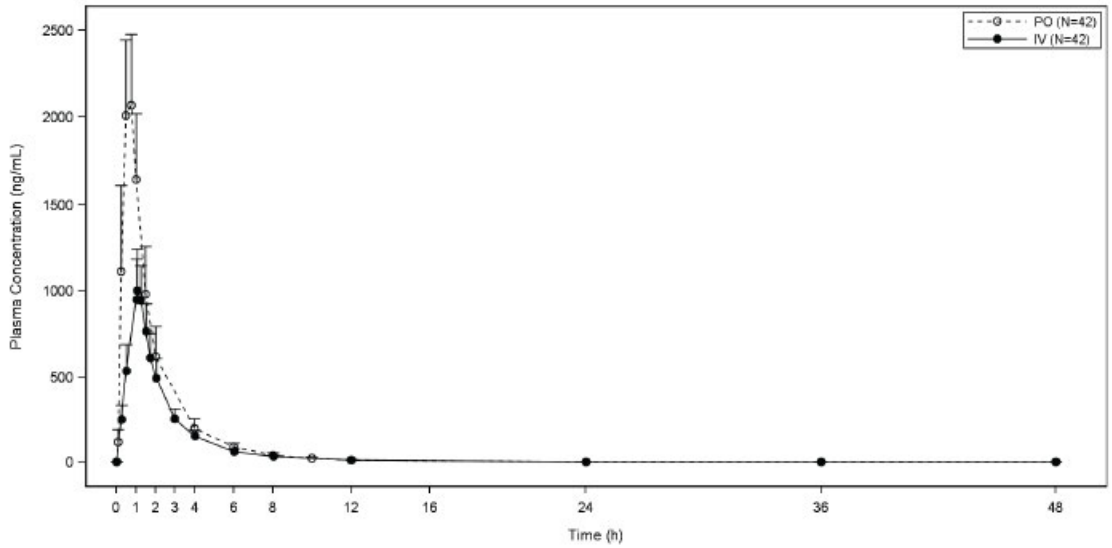
[a]: Median and range
CV: coefficient of variation

Source: MT-1186-J03 study report, Table 11-5, page 66

Edaravone Glucuronide

The mean plasma concentration-time profiles and plasma pharmacokinetic parameters of edaravone glucuronide after administration of edaravone 105 mg oral suspension and edaravone 60 mg/60 min intravenous infusion are shown in **Figure 4** and **Table 5**, respectively.

Figure 4. Mean plasma concentration-time profiles of edaravone glucuronide after administration of edaravone 105 mg oral suspension and edaravone 60 mg/60 min intravenous infusion



Source: MT-1186-J03 study report. Figure 11-3 (Bottom), page 64

Table 5. Plasma pharmacokinetic parameters of edaravone glucuronide after administration of edaravone 105 mg oral suspension and edaravone 60 mg/60 min intravenous infusion

Treatment	Plasma PK parameter	t_{max}[a] (h)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
PO	Mean	0.75	2237	3914	3924	3.75
(N=42)	CV%	0.25, 1.00	17.3	18.6	18.6	14.7
IV	Mean	1.08	1012	2285	2295	3.69
(N=42)	CV%	1.00, 1.27	23.3	21.1	21.0	12.9

[a]: Median and range
CV: coefficient of variation

Source: MT-1186-J03 study report. Table 11-6, page 66

Discussion and Conclusion

Data from all 42 participants were used to calculate pharmacokinetic parameters such as C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$. All 42 subjects were healthy Japanese (28 males and 14 females). This study demonstrated that the 105 mg oral suspension of edaravone has equivalent AUC_{0-t} and $AUC_{0-\infty}$ of unchanged edaravone to the approved 60 mg/60 min IV formulation [Geometric mean ratio (90% CI): 0.974 (0.914-1.038) for AUC_{0-t} and 0.977 (0.917-1.041) for $AUC_{0-\infty}$]. Geometric mean ratio of Cmax of 105 mg oral suspension compared to 60 mg/60 min IV formulation and its lower limit of 90% CI were also within the range of 0.80 to 1.25, while the upper limit of 90% CI exceeded 1.25. [Geometric

mean ratio (90% CI): 1.217 (1.090-1.359)] as shown in **Table 6.** The absolute bioavailability of oral edaravone was found to be 57.3%.

Table 6. Statistical analysis for comparative bioavailability of plasma pharmacokinetics parameter of unchanged edaravone

	Geometric LS mean		Ratio (PO / IV)
Plasma PK parameter	PO	IV	(90% CI)
C_{max} (ng/mL)	1500	1232	1.217 (1.090-1.359)
AUC_{0-t} (ng·h/mL)	1645	1689	0.974 (0.914-1.038)
$AUC_{0-\infty}$ (ng·h/mL)	1665	1704	0.977 (0.917-1.041)

Source: MT-1186-J03 study report. Table 11-4, page 62

Due to the differences in first pass effect, it is expected that metabolic profiles will be different for the two products. To evaluate such difference between two routes of administration, plasma concentrations of unchanged edaravone, edaravone sulfate and edaravone glucuronide were measured. Maximum plasma concentrations (C_{max}) of edaravone sulfate and edaravone glucuronide after edaravone 105 mg oral administration were 1.5-fold and 2.2-fold greater than those observed after edaravone 60 mg/60 min intravenous infusion.(**Table 7**) $AUC_{0-\infty}$ of edaravone sulfate and edaravone glucuronide after edaravone 105 mg oral administration were 1.3-fold and 1.7-fold greater than those observed after edaravone 60 mg/60 min intravenous administration.(Table 8)

Table 7. Pharmacokinetic parameters of edaravone metabolites

Metabolite	Pharmacokinetic parameter	Edaravone 105 mg oral	Edarovone 60 mg/60 min IV infusion	Ratio of Oral/IV
Edaravone sulfate	C_{max} (ng/mL)	7291	4843	1.5
	$AUC_{0-\infty}$ (ng *hr/mL)	20055	15055	1.3
Edaravone glucuronide	C_{max} (ng/mL)	2237	1012	2.2
	$AUC_{0-\infty}$ (ng *hr/mL)	3924	2295	1.7

Source: MT-1186-J03 study report.

Overall, this pivotal BE study (MT-1186-J03) results demonstrated that geometric LS mean ratios of plasma AUC exposures of edaravone after oral and intravenous administration meets the bioequivalence criteria, but not the C_{max}. In addition, both sulfate and glucuronide exposures (C_{max} and AUC) after oral administration were >1.3-fold greater than those after intravenous administration. To justify the observed increase in

exposures for Edaravone and metabolites and evaluate the safety after oral administration, The applicant has conducted a long-term safety study of edaravone 105 mg oral suspension, MT-1186-A01. Its interim results at 24-weeks were submitted with this application. Oral edaravone was well tolerated during the study without serious TEAEs. Please refer to clinical review by Dr. Troiani for further details.

6. Summary of other Clinical Pharmacology Assessments

Clinical studies submitted in the application are listed in **Table 1**. The assessment of the pivotal BE study, MT-1186-J03, is included in **Section 5**. Parts of studies, MT-1186-J01, MT-1186-J02, and MT-1186-J06 evaluated the effect of different meal conditions on the pharmacokinetics of edaravone. Cross study comparison of results from studies, MT-1186-J03, MT-1186-J04, and MT-1186-J05 was performed to determine the effect PEG tube on edaravone pharmacokinetics after its oral administration. Study MT-1186-Z-101 evaluated the pharmacokinetics of edaravone administered in healthy subjects with or without nasogastric tube. One or two cohorts from studies MT-1186-J01 and MT-1186-J02 have evaluated the effect of race on the edaravone pharmacokinetics. Groups 1 in Cohort 1 of the study MT-1186-J02, evaluated clinical DDI of edaravone as inducer of CYP3A4 metabolism, and as inhibitor of BCRP transport. Group 2 in Cohort 1 of the study MT-1186-J02, evaluated clinical DDI of edaravone sulfate as perpetrator of OAT3 transport.

Effect of extrinsic factors

Effect of type and timing of food consumption on the pharmacokinetics of orally administered edaravone

Effect of type and timing of food consumption on the pharmacokinetics of orally administered edaravone was evaluated in Japanese healthy subjects to assess various gastric conditions on the rate and extent of drug absorption. These evaluations were part of three different studies: MT-1186-J01, MT-1186-J02, and MT-1186-J06. The data are summarized and presented in Table 8.

Overall, these studies demonstrated a significant reduction in edaravone plasma exposures when it was taken thirty minutes after high fat meal (1000 calories, 50% fat), four hours after high fat meal, and two hours after low fat meal (400 calories, 25% fat). Additionally, these studies also demonstrated no significant reduction in edaravone exposures when it was taken one hour before high fat meal, eight hours after high fat meal, four hours after low fat meal, and two hours after caloric supplement (250 calories). No significant changes in plasma edaravone sulfate or edaravone glucuronide exposures were observed in any of the studied gastric conditions. In summary, these results suggest that edaravone oral suspension should be taken on empty stomach (overnight fasting of

8 hours) and continue the fasting for at least one hour of post doing. Alternatively, edaravone oral suspension can be administered 2, 4, and 8 hours after consumption of caloric supplement, low-fat meal, and high-fat meal, respectively.

Table 8. Effect of type and timing of food consumption on the pharmacokinetics of orally administered edaravone

Study #; Dose	Edaravone administration relative to type of food consumption	Effect on Cmax	Effect on AUC
MT-1186-J02 N = 9; 100 mg	1 hour before high-fat meal	No significant change	No significant change
MT-1186-J01 N = 6; 200 mg	30 min after high-fat meal	Decreased to 20%	Decreased to 40%
MT-1186-J02 N = 9; 100 mg	4 hours after high-fat meal	Decreased to 52%	Decreased to 74%
MT-1186-J06 N = 16, 105 mg	8 hours after high-fat meal	No significant change	No significant change
MT-1186-J06 N = 16, 105 mg	2 hours after low-fat meal	Decreased to 55%	Decreased to 79%
MT-1186-J06 N = 16, 105 mg	4 hours after low-fat meal	No significant change	No significant change
MT-1186-J06 N = 16, 105 mg	2 hours after caloric supplement (250 calories e.g., ENSURE LIQUID)	No significant change	No significant change

Source: Summary of Clinical pharmacology and Food effect parts of the following study reports; MT-1186-J01, MT-1186-J02, MT-1186-J03, MT-1186-J05, and MT-1186-J06

Effect of PEG tube on unchanged edaravone pharmacokinetics after oral administration

A cross study comparison of results from three studies, MT-1186-J03, MT-1186-J04 and MT-1186-J05, were performed. Study MT-1186-J03 evaluated edaravone pharmacokinetics after oral administration in healthy subjects. Study MT-1186-J04 evaluated edaravone pharmacokinetics in ALS patients after oral administration. Study MT-1186-J05 evaluated edaravone pharmacokinetics in ALS patients after edaravone administration via PEG tube. Edaravone plasma exposures from these three studies are

presented in **Table 9**. PEG tube is inserted through the wall of abdomen directly into the stomach, while nasogastric tube (NGT) carries food and medicine to the stomach through the nose.

Table 9. Effect of PEG tube on the pharmacokinetics of unchanged edaravone after oral administration

Study	Study Population	Dose (mg)	Statistics	t_{max} [a] (h)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
J03 (n=42)	Healthy Subjects	105	Mean	0.50	1656	1762	9.75
			SD	0.25, 0.75	734	540	8.47
J04 (n=9)	Patients with ALS	105	Mean	0.25	1903	1736	6.11
			SD	0.08, 0.50	979	811	1.17
J05 (n=6)	ALS patients with PEG tube	105	Mean	0.29	2163	2310	4.47
			SD	0.25, 0.50	902	954	0.45

Source: Summary of Clinical Pharmacology studies, Table 2.7.2.3-3, page 65

Additionally, pharmacokinetic profiles of edaravone after administration after oral or via nasogastric tube were investigated in a phase 1 open-label, single-dose, crossover study in 36 healthy subjects (Study MT-1186-Z-101). Pharmacokinetic parameters and exposure levels of unchanged edaravone are presented in **Table 10**

Table 10. Relative ratio of exposures and PK parameters of oral vs nasogastric tube administration

	Geometric LS mean		Ratio (NGT / PO)
Plasma PK parameter	PO	NGT	(90% CI)
C_{max} (ng/mL)	2310	2431	1.052 (0.903-1.227)
AUC_{0-t} (ng·h/mL)	2508	2476	0.987 (0.936-1.041)
$AUC_{0-\infty}$ (ng·h/mL)	2551	2501	0.981 (0.931-1.033)

Source: Study Report MT-1186-Z101, Table 11-3, page 56

Study MT-1186-Z-101 demonstrated that the nasogastric tube administration has a similar C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ to the oral route (geometric LS mean ratio [90%CI]: 1.052 [0.903-1.227], 0.987 [0.936-1.041], and 0.981 [0.931- 1.033], respectively).

Results from the studies: MT-1186-J03, MT-1186-J04, MT-1186-J05, and MT-1186-Z-101 demonstrated that plasma exposure parameters C_{max} and AUC are in similar range between healthy subjects with or without nasogastric tube and ALS patients with or without PEG tube. These results suggest that edaravone can be administered via PEG/NG tube without the need for dose adjustment and no significant change in plasma pharmacokinetics.

Clinical Drug-Drug Interactions studies

In-vitro data indicated a potential for edaravone to induce CYP3A4 and inhibit BCRP, and for the sulfate conjugate to inhibit OAT3 transporter. To further evaluate and corroborate these *in-vitro* results, the applicant has conducted a clinical study to evaluate the drug interactions, safety, and tolerability of sildenafil, rosuvastatin, or furosemide when coadministered with oral edaravone in healthy males in a phase 1 study, MT-1186-J02.

This was an open-label, add-on study with single dose of victim drugs; rosuvastatin 10 mg (BCRP substrate was coadministered with edaravone in Cohort 1, period III, day 9), sildenafil 50 mg (CYP3A4 substrate was coadministered with edaravone in Cohort 1, period III, day 12) or furosemide 40 mg (OAT3 substrate was coadministered with edaravone in Cohort 2, period II, day 6). There were no clinically relevant differences in the mean C_{max} and AUC of rosuvastatin, sildenafil and furosemide (victim drugs) between the administration of victim drug alone and the coadministration with edaravone.

Effect of Edaravone on PK of Sildenafil

LS mean and ratios for PK parameters of sildenafil following the oral administration of sildenafil 50 mg alone and the oral coadministration with edaravone 120 mg are presented in **Table 11**

Table 11. statistical analysis of effect of coadministration with edaravone on PK parameters of sildenafil

Parameter (unit)	LS Mean		Ratio	90% CI for Ratio	
	Sildenafil + Edaravone (N=31)	Sildenafil alone (N=31)	(Sildenafil + Edaravone / Sildenafil alone)	Lower	Upper
C_{max} (ng/mL)	183.07	194.29	0.9422	0.8047	1.1032
AUC_{0-t} (ng·h/mL)	438.57	469.76	0.9336	0.8750	0.9961
$AUC_{0-\infty}$ (ng·h/mL)	449.79	482.83	0.9316	0.8750	0.9918

Source: MT-1186-J02 Study Report. Table 11-6, page 101

Effect of Edaravone on PK of Rosuvastatin

The LS mean and ratio for PK parameters of rosuvastatin following the oral administration of rosuvastatin 10 mg alone and the oral coadministration with edaravone 120 mg are presented in **Table 12**.

Table 12. statistical analysis of effect of coadministration with edaravone on PK

Parameter (unit)	LS Mean		Ratio	90% CI for Ratio	
	Rosuvastatin + Edaravone (N=31)	Rosuvastatin alone (N=32)	(Rosuvastatin + Edaravone / Rosuvastatin alone)	Lower	Upper
C_{max} (ng/mL)	10.37	10.60	0.9789	0.9056	1.0581
AUC_{0-t} (ng·h/mL)	146.66	140.20	1.0461	0.9855	1.1105
$AUC_{0-\infty}$ (ng·h/mL)	155.19	151.59	1.0237	0.9684	1.0822

Source: MT-1186-J02 Study Report. Table 11-4, page 99

Effect of Edaravone on PK of Furosemide

LS mean and ratio for PK parameters of furosemide following the oral administration of furosemide 40 mg alone and the oral coadministration with edaravone 120 mg are presented in Table 13

Table 13. Statistical analysis of effect of coadministration with edaravone on PK parameter of furosemide

Parameter (unit)	LS Mean		Ratio	90% CI for Ratio	
	Furosemide + Edaravone (N=34)	Furosemide alone (N=34)	(Furosemide + Edaravone / Furosemide alone)	Lower	Upper
C_{max} (ng/mL)	1627.42	1502.80	1.0829	0.9568	1.2257
AUC_{0-t} (ng·h/mL)	3814.03	3683.84	1.0353	0.9776	1.0965
$AUC_{0-\infty}$ (ng·h/mL)	3838.74	3724.20	1.0308	0.9754	1.0892

Source: MT-1186-J02 Study Report. Table 11-8, page 103

Reviewer's assessment

The 90% CIs for parameters of each substrate were within the prespecified threshold for equivalence (0.80-1.25). Hence, it was determined that edaravone has no meaningful effect on CYP3A4 induction, or BCRP and OAT3 inhibition, and does not alter the PK of these substrates.

Effect of intrinsic factors

Effect of race (Japanese vs Caucasian) on the pharmacokinetics of edaravone

The effect of race on the pharmacokinetics of orally administered edaravone pharmacokinetics were evaluated in two phase 1 studies: MT-1186-J01 and MT-1186-J02. No remarkable difference between racial populations in each parameter were noted

in both studies. These data suggest that pharmacodynamics observed in one population may be extrapolated to the other population with respect to PK.

Effect of Edaravone on QT prolongation

Based on the results of the QT study and the pivotal BE study, the applicant concluded that, “at a dose of 5 times the recommended dose, edaravone does not prolong the QT interval to any clinical relevant extent”. The Interdisciplinary Review Team for Cardiac Safety (QT-IRT) was consulted requesting their scientific opinion on the applicant’s conclusion.[4] QT-IRT in their response agreed with the sponsor’s conclusion. Further, the QTIRT team concluded that the observed small increase in metabolite concentrations after oral administration is not expected to result in QT risk. Please refer to the QT review by Dr. Kitabi.[5]

[4] QT-IRT consult request in DARRTS dated February 28, 2022

[5] QT-IRT Review in DARRTS dated March 14, 2022

7. Appendix

A liquid chromatography/tandem mass spectrometry (LC-MS/MS) method was developed and validated for the determination of edaravone and its metabolites in human plasma. Method details and validation results were included in the study report NB17011V.

LC-MS/MS method for edaravone in plasma and its validation summary:

Analytes and Internal standard	MCI-186 (Edaravone) with 99.89% purity (lot # Y0144191A), was supplied by Mitsubishi Tanabe Pharma Corporation. ^{13}C-MCI-186 (Internal standard) with 99.28% purity (Lot # E1938004A) was supplied by Mitsubishi Tanabe Pharma Corporation.
Selectivity	Both edaravone and internal standard were eluted approximately 3.2 minutes with interfering peaks in bank and samples. Total run time was five minutes.
Linearity of calibration curve and quantification range	Calibration curve for edaravone quantification in human plasma was established between 1 to 2000 ng/mL with good linearity and reproducibility.
Accuracy	Edaravone accuracy at LLOQ was 99.6% to 101.0% Edaravone accuracy at other concentrations was 94.6% to 104.2 %
Recovery	Percent recovery for edaravone was 91.1 -103% Percent recovery for Internal standard was 96.5 %
Dilution integrity	Edaravone samples were tested with 10-fold diluted samples with human plasma. Diluted samples were detected with 2% precision and 93.8% accuracy.
Stability in the composite matrix at −20°C and −80°C	Edaravone and internal standard were found to be stable in the composite matrix for at least 109 days.
Stability in the composite matrix after freeze/thaw cycles	Edaravone and internal standard were found to be stable after 3 freeze/thaw cycles.
Stability in injection samples at 4°C after pretreatment	Edaravone in injection samples was found to be stable for 72 hours at 4°C.
Stability in the composite matrix on ice	Edaravone and the internal standard were found to be stable in the matrix for four hours on ice.
Stability in the composite matrix at room temperature	Edaravone and the internal standard were found to be stable in the matrix for four hours at room temperature.

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/s/

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