Original Manuscript

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

Clinical Pharmacology
in Drug Development
2021, 10(10) 1188–1197

DOI: 10.1002/cpdd.952

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Abstract

The neuroprotective agent edaravone is an intravenous treatment for amyotrophic lateral sclerosis. As intravenous administration burdens patients, orally administered treatments are needed. This phase 1, open-label, single-dose crossover study in 42 healthy adults evaluated bioequivalence of a 105-mg edaravone oral suspension and intravenous edaravone (60 mg/60 min). The evaluation was whether the 90% confidence intervals (CIs) for the ratio of the maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve from time 0 to the last quantifiable time point and to infinity of unchanged edaravone were between the bioequivalence limit of 0.80 and 1.25. Metabolic profiles and elimination pathways were also compared between the 2 routes. Geometric mean ratios and 90%CIs of area under the plasma concentration–time curve from time 0 to the last quantifiable time point and to infinity for unchanged edaravone satisfied bioequivalence limits. The geometric mean ratio and its lower limit of 90%CI of C_{max} of the 105-mg oral suspension compared with 60-mg intravenous formulations for unchanged edaravone fell within bioequivalence limits. Both formulations showed triphasic plasma concentration–time profiles of unchanged edaravone after reaching C_{max}. Plasma concentrations of edaravone inactive metabolites after oral administration were higher than with intravenous administration. Edaravone in both routes underwent urinary excretion, mainly as the glucuronide conjugate and, to a lesser extent, as the sulfate conjugate. Urinary excretion of unchanged edaravone was low, and urinary relative composition ratios of unchanged edaravone and metabolites were similar for both formulations. These findings showed equivalent exposure of the 105-mg oral suspension of edaravone to the 60-mg intravenous formulation, supporting further investigation of the oral suspension for treating amyotrophic lateral sclerosis.

Keywords

ALS, amyotrophic lateral sclerosis, bioequivalence study, clinical pharmacology, edaravone, oral formulation

The neuroprotective agent edaravone acts as a free radical scavenger to eliminate lipid peroxides and hydroxyl radicals, which is thought to mitigate oxidative injury predominantly in the motor neurons.[1] Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disorder of the motor neurons ultimately resulting in death due to respiratory paralysis,[2] and patients with ALS are similar, in terms of demographic and clinical characteristics, between Western and Japanese populations.[3]

Edaravone 60 mg is an ALS treatment used in several countries and is administered intravenously over a 60-minute duration once per day. The first cycle consists of 14 consecutive dosing days followed by a 14-day drug-free period. Each subsequent cycle consists of daily dosing for 10 days out of a 14-day period with a 14-day drug-free period. The efficacy and safety of edaravone for ALS was demonstrated in several clinical trials.[4–14] Notably, the effect of edaravone on functional loss of

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Submitted for publication 7 December 2020; accepted 22 March 2021.

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Clinical trial registration: NCT04493281

motor neurons differentiates it from other treatments for ALS that provide only symptomatic effects.[3,15] In a pivotal phase 3 clinical study, the primary efficacy end point of the 24-week ALS Functional Rating Scale–Revised score was significantly improved ($P = .001$) in patients with ALS who received edaravone compared with placebo, indicating reduced functional loss in edaravone-treated patients.[14]

The pharmacokinetic (PK) characteristics of intravenous (IV) edaravone have been described previously.[16] Metabolism in the liver and kidneys produces pharmacologically inactive sulfate and glucuronide conjugates, and excretion is predominantly urinary as the glucuronide conjugate (70%-90% of the dose). Population PK analyses have suggested a trend of nonlinear clearance (CL) of IV edaravone.[17] Recent PK studies using IV edaravone revealed a more than dose-proportional increase in maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) in the dose range of 30 to 300 mg.[18–20]

IV administration of edaravone places a large additional burden on patients with ALS, as well as on their families and their healthcare providers, which is primarily associated with frequent injections and the need for repeated hospital attendance and/or caregiver visits. Thus, there is a clinical need for oral agents for the treatment of ALS, and there is now ongoing research into oral administration of edaravone. In phase 1 studies[18,21] in healthy volunteers, an increase in plasma exposure greater than the dose ratio of an oral suspension of edaravone was observed, and an oral dose of 100 to 105 mg was predicted to produce an AUC equivalent to that of the approved 60 mg/60 min edaravone IV formulation. However, the composition and dose of the edaravone oral suspension bioequivalent to the edaravone IV formulation for ALS treatment remains to be fully clarified. Therefore, the purpose of this study was to evaluate the bioequivalence between the IV and oral suspension of edaravone and to determine the dose of the oral suspension of edaravone with equivalent plasma exposures to IV edaravone in healthy subjects. In addition, similarities in the metabolic profiles and elimination pathway after IV and oral edaravone administration were investigated.

Methods

Ethics

The study was conducted at P-one Clinic, Keikokai Medical Corporation (Tokyo, Japan). Before study initiation, the protocol and all other appropriate documents were reviewed and approved by the Institutional Review Board of P-one Clinic, Keikokai Medical Corporation. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki; the Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices; Good Clinical Practice; and the protocol. All subjects provided written consent for participation.

Subjects

The study was conducted in healthy Japanese men and women between 20 and 45 years of age. Key exclusion criteria included a body mass index of <18.0 or >30.0 kg/m^2 or a body weight of <50 kg; a previous history of cardiac, hepatic, renal, gastrointestinal, respiratory, psychiatric/nervous, hematopoietic, or endocrine diseases; a positive test for hepatitis B surface antigen, serologic test for syphilis, hepatitis C virus antibody, or HIV antigen/antibody; and any clinically significant abnormalities in laboratory tests. Subjects were also excluded if they had used drugs other than acetylsalicylic acid (single use) and/or nutritional supplements within 7 days before the study start; had alcohol or any products containing xanthine or caffeine, grapefruit, grapefruit juice, or any processed food(s) containing these substances; and/or used tobacco or any products containing nicotine within 24 hours before screening and the visit on day −1.

Study Design

This was a single-dose, randomized, 2-period, 2-sequence crossover, open-label phase 1 study to evaluate the bioequivalence of an oral suspension and IV formulation of edaravone in healthy subjects by assessing each PK parameter with the bioequivalence limit.

Intervention

A commercially available product of edaravone (RADICUT BAG for IV infusion 30 mg; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) was used for the IV formulation. The composition of the edaravone oral suspension is summarized in Table 1. A 105-mg dose of edaravone oral suspension was selected for assessment so it would provide an AUC corresponding to those of the approved 60-minute IV infusion of edaravone 60 mg,[18] as predicted in previous studies.[21] Specifically, using a 4-parameter logistic model developed with the relationship between the AUC from time 0 to infinity ($AUC_{0-\infty}$) with extrapolation of the terminal phase values and oral doses with the range of 30 to 300 mg of edaravone, the predicted $AUC_{0-\infty}$ values after administration of 100- and 105-mg oral doses would be 0.97-fold (90% confidence interval [CI], 0.84-1.11) and 1.06-fold (90%CI, 0.91-1.20), respectively, compared with that of 60-mg IV edaravone.[21] After oral administration of

Table 1. Composition of the Edaravone Oral Suspension

Ingredient	Content
Edaravone	105 mg
Polyvinyl alcohol	5 mg
Xanthan gum	15 mg
Sodium bisulfite	5 mg
l-Cysteine hydrochloride hydrate	2.5 mg
Sodium hydroxide	q.s.[a]
Phosphoric acid	q.s.[a]
Simethicone emulsion	2.5 mg
d-Sorbitol	2000 mg
Purified water	q.s.
Total	5 mL

q.s., quantum sufficient.
[a]pH adjustment to achieve pH 4.0-4.5 in the final formulation.

these doses, C_{max} was predicted to be beyond that of 60-mg IV edaravone. To achieve sufficient exposures of edaravone in plasma for subsequent treatment effects and to prevent the AUC and C_{max} of the oral suspension from falling short of respective values of IV edaravone, the 105-mg dose was considered preferable, based on the AUC and C_{max} values and their 90%CI of oral doses estimated from model analysis. The $AUC_{0-\infty}$ and C_{max} of 60-mg IV edaravone were calculated to be 1738 ng·h/mL and 1195 ng/mL, respectively.[18] The $AUC_{0-\infty}$ and C_{max} of 105-mg edaravone oral suspension were estimated to be 1828 ng·h/mL and 1661 ng/mL, respectively.[21] Therefore, subjects under fasted conditions in group 1 received the 105-mg edaravone oral suspension in period I and the 60 mg/60 min edaravone IV formulation in period II. Subjects under fasted conditions in group 2 received the 60 mg/60 min edaravone IV formulation in period I and the 105-mg edaravone oral suspension in period II (Figure S1).

Objectives and Outcomes

Blood and urine samples were collected for measurement of plasma and urine concentrations, respectively, of unchanged edaravone and its sulfate and glucuronide conjugates. Blood samples for PK measurement were obtained before dosing; at 5, 15, 30, and 45 minutes; and at 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, and 48 hours after oral administration. For IV administration, blood samples for PK measurement were obtained before dosing; at 15 and 30 minutes; and at 1, 1.083, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after dosing. Urine samples were collected by voluntary urination until 48 hours after dosing, and before study drug administration and at 24 and 48 hours after dosing by forced voiding.

Processing of blood samples and separation of plasma were performed on ice. After sampling, blood was transferred into stabilizer-containing tubes and subjected to centrifugation at 4°C, 1500 × *g* for 10 minutes. A prespecified quantity of plasma was placed into a tube with a fixed quantity of internal standard, stabilizer, and buffer, and stored at −70°C or below to await assay. Urine was collected and dispensed into urine storage tubes containing stabilizer; samples were frozen until processing.

For unchanged edaravone and edaravone sulfate conjugate in both plasma and urine samples, frozen samples were thawed in iced water and treated with extraction solvent for 10 minutes at room temperature. The aqueous layer was frozen using dry ice–acetone, and the entire organic layer was evaporated to dryness under a 45°C nitrogen stream. Following reconstitution, the entire solution was used for liquid chromatography–mass spectrometry injection. To determine the concentration of edaravone sulfate conjugate, the samples underwent hydrolysis and the determined edaravone concentrations were then converted to concentrations of edaravone sulfate conjugate. For edaravone glucuronide conjugate in both plasma and urine, frozen samples were thawed in iced water and extracted with solid-phase sorbent. The solution was evaporated to dryness under a 40°C nitrogen stream. Following reconstitution, the sample was transferred for liquid chromatography–mass spectrometry injection.

Plasma and urine concentrations of unchanged edaravone and its metabolites were assessed with validated methodologies; values below the lower limit of quantification were designated as 0. Further details regarding the bioanalytical assays are shown in Table S1. All assays to determine plasma and urine concentrations were conducted by Sumika Chemical Analysis Service, Ltd. (Osaka, Japan).

PK parameters evaluated for unchanged edaravone after both IV and oral administration were AUC from time 0 to the last quantifiable concentration time point (AUC_{0-t}), $AUC_{0-\infty}$, C_{max}, time to reach C_{max} (t_{max}), terminal elimination half-life ($t_{1/2}$), bioavailability, total CL or apparent CL after oral administration, urinary excretion ratio of drug from time 0 to 48 hours, and renal clearance. Volume of distribution at steady state and volume of distribution during the terminal phase were evaluated for IV edaravone. For sulfate and glucuronide conjugates, assessments included AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{1/2}$. PK analysis was conducted for all subjects who received ≥1 dose of edaravone oral suspension or edaravone IV and who had evaluable PK data.

Safety assessments included adverse events (AEs), serious AEs, adverse drug reactions (ADRs), and serious ADRs. The safety analysis set consisted of all subjects who received ≥1 dose of edaravone oral suspension or edaravone IV.

Statistical Methods

Sample size calculation was based on the $AUC_{0-\infty}$ and C_{max} data for unchanged drug obtained in previous studies,[18,21] as described below. The calculation was performed so that for $AUC_{0-\infty}$, the 2-sided 90%CI of the mean ratio of edaravone oral suspension to edaravone IV would fall within the bioequivalence criterion of 0.80 to 1.25; and for C_{max}, the lower limit of the 2-sided 90%CI would exceed 0.80. The intraindividual standard deviations of log-transformed $AUC_{0-\infty}$ and C_{max} were assumed to be 0.232 and 0.706, respectively, from the previous study.[21] Assuming that the expected ratios of $AUC_{0-\infty}$ and C_{max} of edaravone oral suspension to edaravone IV were 1.06 and 1.40 from the 4-parameter logistic model, the necessary total numbers of subjects calculated on the basis of 2 one-sided tests with a significance level of 5% and power ≥90% were 36 and 24, respectively. Accordingly, sample size was set at 42 with 21 subjects per group to allow 36 subjects to complete the 2 periods.

For assessment with the bioequivalence limit, the analysis of variance was conducted for the log-transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of unchanged edaravone, which included factors accounting for the following sources of variation: sequence, subjects nested in sequences, period, and treatment. Estimates of the mean difference between formulations (oral suspension minus IV formulation) on the log scale and 90%CI for the difference were back transformed to present mean ratios and their 90%CIs for oral suspension to IV formulation. The estimated 90%CIs of the geometric mean ratios were examined to lay entirely within the standard bioequivalence limits of 0.80 and 1.25. For reference, the same analysis was also performed on other PK parameters of unchanged edaravone, such as t_{max}, AUC from time 0 up to the last sampling time point for all time points, and elimination rate constant from the central compartment (K_{el}). Values of t_{max} were not log-transformed prior to statistical analysis.

Results

Subject Disposition and Characteristics

The study included 42 subjects (n = 21 in each group). The baseline demographic characteristics of the study population are summarized in Table 2. Two-thirds of subjects were male in both study groups. The mean ± standard deviation age was 33.1 ± 7.4 years, body weight was 63.4 ± 7.9 kg, and body mass index was 22.7 ± 2.2 kg/m^2.

Plasma Concentrations of Unchanged Edaravone

The results for the plasma concentration of unchanged edaravone for the oral suspension and IV formulation are summarized in Table 3 and Figure 1. Both oral and IV formulations showed similar concentration-time profiles with rapid increase until C_{max} within 1 hour and almost comparable elimination consisting of 3 phases after reaching C_{max}. Slight differences were observed around C_{max} due to differences in oral absorption and IV infusion.

Table 2. Demographic Characteristics of Subjects

	Total (N = 42)
Sex, male	28 (66.7)
Age, y	33.1 ± 7.4
Height, cm	166.9 ± 7.0
Weight, kg	63.4 ± 7.9
Body mass index, kg/m^2	22.7 ± 2.2
Race, Japanese	42 (100)

Data are presented as mean ± standard deviation or n (%).

Assessment of Bioequivalence

The statistical analysis with bioequivalence limit for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of unchanged edaravone, and the geometric mean ratios and 90%CIs of unchanged edaravone between the 2 formulations are summarized in Table 4. The statistical analysis revealed that the oral suspension of edaravone 105 mg had an equivalent AUC_{0-t} and $AUC_{0-\infty}$ to the IV formulation of edaravone 60 mg (geometric mean ratio [90%CI], 0.97 [0.91-1.04] and 0.98 [0.92-1.04], respectively). The geometric mean ratio of C_{max} of the 105-mg oral suspension compared to the 60-mg IV formulation was within prespecified limits, but the upper limit of 90%CI exceeded 1.25 (geometric mean ratio [90% CI], 1.22 [1.09-1.36]). For other PK parameters, the geometric mean ratios and 90%CIs of unchanged edaravone between the 2 formulations were 0.98 (90% CI 0.92-1.04) for AUC from time 0 up to the last sampling time point for all time points and 0.94 (90% CI 0.76-1.15) for K_{el}. The least squares mean difference and 90%CI for t_{max} (the 105-mg oral suspension minus the 60-mg IV formulation) was −0.56 (90%CI, −0.60 to −0.51).

Plasma Concentration of Edaravone Metabolites

The plasma PK parameters and concentration-time profiles for the edaravone sulfate and glucuronide conjugates following administration of the 105-mg edaravone oral suspension and 60-mg edaravone IV formulation are summarized in Table 5 and Figure 2. The mean plasma concentrations of both sulfate and glucuronide conjugates with the 105-mg oral suspension were higher than those with the 60-mg IV formulation (1.3- and 1.7-fold higher in AUC, respectively), but the shape of the profiles and elimination patterns were similar between the 2 formulations after reaching C_{max}.

Table 3. Plasma PK Parameters of Unchanged Edaravone

Treatment (N = 42)	Plasma PK Parameter	t_{max}[a], h	C_{max}, ng/mL	$AUC_{0\text{-}t}$, ng·h/mL	$AUC_{0\text{-}\infty}$, ng·h/mL	$t_{1/2}$, h	F, %	V_{ss}, L	V_z, L	CL[b], L/h
Oral (105 mg)	Arithmetic mean	0.5	1656	1743	1762	9.75	57.3	...	...	67.9
	CV%	0.3-0.8	44.3	30.7	30.6	86.9	21.9	...	...	44.4
IV (60 mg)	Arithmetic mean	1.0	1253	1720	1736	8.82	...	63.1	418	35.9
	CV%	1.0-1.0	18.3	18.9	19.1	94.4	...	34.9	76.7	20.9

AUC, area under the plasma concentration–time curve; $AUC_{0\text{-}\infty}$, AUC from time 0 to infinity; $AUC_{0\text{-}t}$, AUC from time 0 to the last quantifiable time point; CL, total clearance; C_{max}, maximum plasma concentration after administration; CV%, coefficient of variation percentage; F, bioavailability calculated from ratio of $AUC_{0\text{-}\infty}$; IV, intravenous; PK, pharmacokinetic; $t_{1/2}$, half-life; t_{max}, time to reach C_{max}; V_{ss}, volume of distribution at steady state; V_z, volume of distribution during terminal phase.
[a] Median and range.
[b] Apparent CL after oral administration.

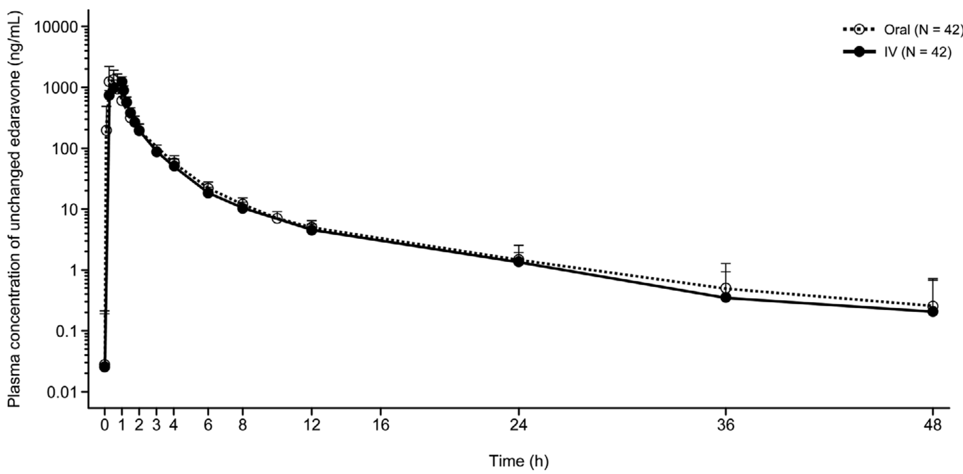

Figure 1. Mean plasma concentration–time profiles of unchanged edaravone for the 105-mg oral suspension and the 60-mg IV formulation (log-linear plot). Data are shown as mean + standard deviation. IV, intravenous.

Table 4. Statistical Analysis of Bioequivalence of Plasma PK Parameters of Unchanged Edaravone

Plasma PK Parameter	Geometric Mean Oral (105 mg)	Geometric Mean IV (60 mg)	Ratio, Oral/IV (90%CI)
C_{max}, ng/mL	1500	1232	1.22 (1.09-1.36)
$AUC_{0\text{-}t}$, ng·h/mL	1645	1689	0.97 (0.91-1.04)
$AUC_{0\text{-}\infty}$, ng·h/mL	1665	1704	0.98 (0.92-1.04)

AUC, area under the plasma concentration–time curve; $AUC_{0\text{-}\infty}$, AUC from time 0 to infinity; $AUC_{0\text{-}t}$, AUC from time 0 to the last quantifiable time point; C_{max}, maximum plasma concentration after administration; CI, confidence interval; IV, intravenous; PK, pharmacokinetic.

Urinary Excretion

Urine PK parameters of unchanged edaravone, of the sulfate conjugate, of the glucuronide conjugate, and of unchanged edaravone and the metabolites combined after administration of the 105-mg oral suspension and 60-mg IV formulation are outlined in Table 6. Edaravone was eliminated into urine mainly as glucuronide conjugate and to a lesser extent as sulfate conjugate after administration of both the 105-mg oral suspension and the 60-mg IV formulation. The urinary excretion of unchanged edaravone was low, and the composition ratios of unchanged edaravone and the metabolites in urine were similar for both administration routes.

Safety

One subject in each group experienced an AE, which included aspartate aminotransferase increased in group 1 (oral→IV) and constipation in group 2 (IV→oral). Both AEs were mild in severity, both subjects recovered, and neither were judged by the investigator as related to edaravone. No ADRs, serious AEs, serious ADRs, or AEs leading to study discontinuation occurred.

Discussion

This study shows for the first time that the composition and dose of the 105-mg edaravone oral suspension provides equivalent plasma exposure (with respect to AUC) to that of the IV dosing regimen of 60-mg edaravone for the treatment of ALS. After administration of either the 105-mg oral suspension or 60-mg

Table 5. Plasma PK Parameters of Sulfate Conjugate and Glucuronide Conjugate

Treatment (N = 42)	Plasma PK Parameter	t_{max},[a] h	C_{max}, ng/mL	$AUC_{0\text{-}t}$, ng·h/mL	$AUC_{0\text{-}\infty}$, ng·h/mL	$t_{1/2}$, h
Sulfate conjugate						
Oral (105 mg)	Arithmetic mean	0.8	7291	20 031	20 055	5.8
	CV%	0.5-1.0	26.0	26.2	26.2	32.1
IV (60 mg)	Arithmetic mean	1.1	4843	15 024	15 055	7.6
	CV%	1.0-1.3	16.9	23.8	23.8	31.5
Glucuronide conjugate						
Oral (105 mg)	Arithmetic mean	0.8	2237	3914	3924	3.8
	CV%	0.3-1.0	17.3	18.6	18.6	14.7
IV (60 mg)	Arithmetic mean	1.1	1012	2285	2295	3.7
	CV%	1.0-1.3	23.3	21.1	21.0	12.9

AUC, area under the plasma concentration–time curve; $AUC_{0\text{-}\infty}$, AUC from time 0 to infinity; $AUC_{0\text{-}t}$, AUC from time 0 to the last quantifiable time point; C_{max}, maximum plasma concentration after administration; CV%, coefficient of variation percentage; IV, intravenous; PK, pharmacokinetic; $t_{1/2}$, half-life; t_{max}, time to reach C_{max}.
[a] Median and range.

Table 6. Urine PK Parameters of Unchanged Edaravone and of the Sulfate and Glucuronide Conjugates

Urine PK Parameter	Treatment (N = 42)	Oral (105 mg)	IV (60 mg)
Unchanged edaravone			
Ae% (% of dose)	Arithmetic mean	0.6	0.9
	CV%	31.7	29.0
CL_r, L/h	Arithmetic mean	0.4	0.3
	CV%	53.4	36.6
Sulfate conjugate			
Ae% (% of dose)	Arithmetic mean	6.6	8.1
	CV%	86.4	91.1
Glucuronide conjugate			
Ae% (% of dose)	Arithmetic mean	59.8	78.4
	CV%	15.1	14.6
Unchanged edaravone and metabolites combined			
Ae% (% of dose)	Arithmetic mean	67.0	87.3
	CV%	12.5	10.8

Ae%, urinary excretion ratio of drug from time 0 to 48 hours; CL_r, renal clearance; CV%, coefficient of variation percentage; IV, intravenous; PK, pharmacokinetic.

IV formulation, unchanged edaravone in plasma was eliminated in a triphasic manner after C_{max} was attained. Independent of the route of administration, a similar plasma concentration–time profile of unchanged edaravone was observed. In addition to the equivalent $AUC_{0\text{-}\infty}$ and $AUC_{0\text{-}t}$ with the 60-mg IV formulation, and ratio of C_{max} between the 60-mg IV and 105-mg oral formulations being close to the bioequivalence limit, the 90%CIs for the geometric mean ratio for K_{el} were almost within the bioequivalence acceptance range. Thus, these findings demonstrated that the plasma concentration–time course of unchanged edaravone was very similar between the 105-mg oral suspension and 60-mg IV formulation of edaravone. For t_{max}, a mean difference was observed between the 105-mg oral and 60-mg IV formulations of 0.56 hour; however, the 2 formulations both showed rapid achievement of C_{max} (ie, within 1 hour).

Regarding these findings, it is not common to compare the bioequivalence between IV and orally administered formulations, as these routes of administration do not necessarily show similar characteristics for drug concentration-time profiles. Our findings for edaravone allowed administration of the 105-mg oral formulation to achieve a concentration profile similar to that of the 60-mg IV infusion. Additionally, it was shown that the AUCs of the 2 formulations satisfied the bioequivalence criteria and the ratio and its 90%CI of the 105-mg oral suspension to the 60-mg IV formulation for C_{max} was above the lower bound of the bioequivalence limit. As one of the factors contributing to the equivalent exposures between 2 formulations, edaravone was considered to remain sufficiently soluble to be orally absorbed using the 105-mg oral suspension formulation used in this study, followed by rapid absorption from the gastrointestinal tract to systemic blood. The dose of oral edaravone was planned appropriately for the equivalent plasma exposures considering the nonlinearity of the PK of oral edaravone based on the statistically meaningful calculations, which was previously determined.[21]

This study was also the first to assess the bioavailability of the oral suspension of edaravone in humans, which was found to be 57% at the 105-mg dose compared to the 60-mg IV edaravone dose. Additionally, the urinary excretion ratio of the sum of unchanged edaravone and its metabolites after oral administration compared to IV administration found that the percentage of oral edaravone absorbed was ≥77%, suggesting good absorption from the gastrointestinal tract, which was consistent with data from *in vitro* nonclinical studies.[22]

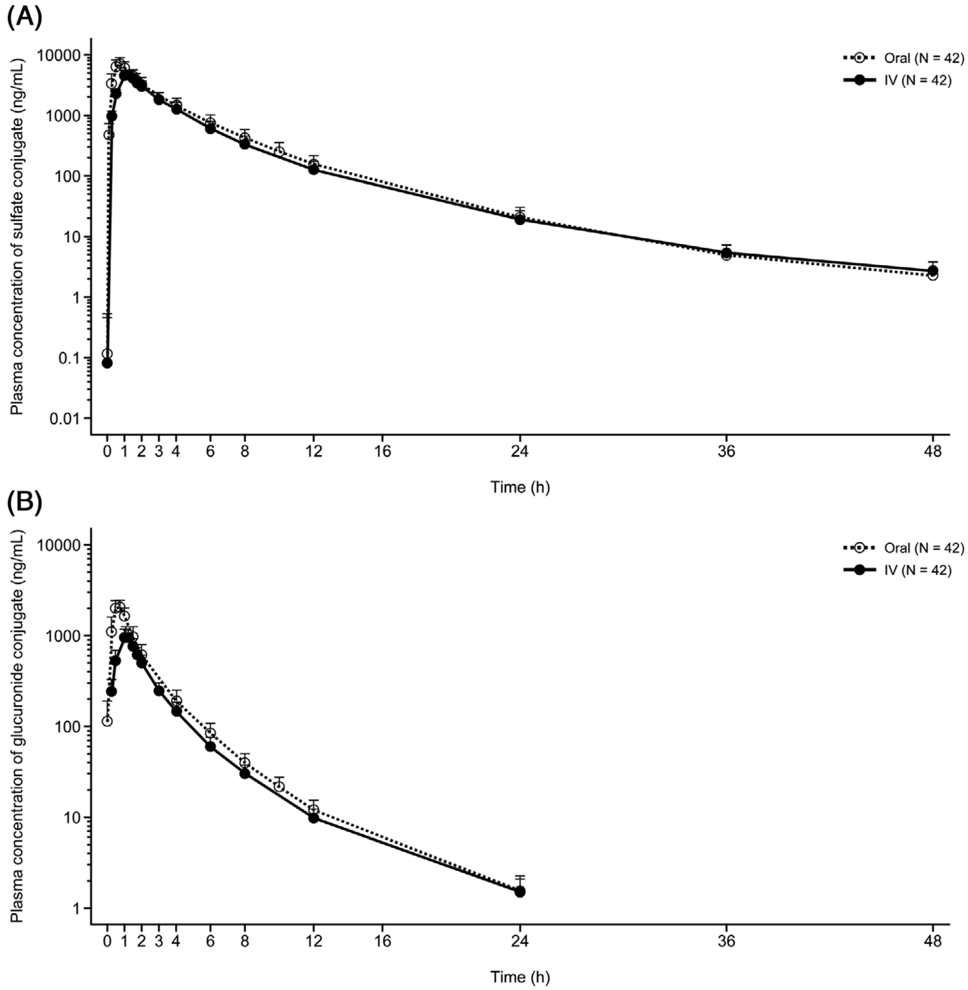

Figure 2. Mean plasma concentration-time profiles of sulfate conjugate (A) and glucuronide conjugate (B) for the 105-mg oral suspension or the 60-mg IV formulation (log-linear plot). Data are shown as mean + standard deviation. IV, intravenous.

For C_{max}, the upper limit of the 90%CI for the geometric mean ratio of the 105-mg oral suspension compared with the 60-mg IV formulation of edaravone slightly exceeded the upper limit of the bioequivalence acceptance range. The higher C_{max} obtained with the oral suspension is considered not to cause clinically relevant safety issues, as the safety margin is high enough compared with the exposure limit obtained in the nonclinical toxicity study,[23] and the safety of edaravone at higher concentrations in humans has been confirmed through the clinical development of the 60-mg IV formulation.[17,22] Furthermore, phase 1 studies conducted at oral edaravone doses from >105 mg to 300 mg support the safety of higher concentrations, as no tolerability or toxicity concerns were identified.[21]

Various causes have been reported for the selective degeneration and loss of motor neurons in ALS, including mechanisms involving oxidative stress and vascular endothelial and glial cells.[24,25] Edaravone, a free radical scavenger, protects motor neurons from oxidative stress by primarily eliminating free radical species and peroxynitrite[1] and may delay disease progression through its motor neuron protective effects via the reduction of oxidative stress in vascular endothelial and glial cells. These effects are thought to be the result of the action of edaravone in blood and in tissues, including cerebrospinal fluid, in which edaravone is rapidly distributed. Nonclinical PK results have shown that edaravone entering the systemic circulation after IV administration is rapidly distributed into tissues and that the concentration of edaravone in the cerebrospinal fluid reaches almost a steady-state level 15 minutes after administration at 50% to 65% of the concentration compared to the plasma concentration from 15 minutes to 3 hours after administration.[26] If the 105-mg oral suspension of edaravone then achieves plasma edaravone concentrations comparable to those of the 60-mg edaravone IV formulation, as was shown in our study, the equivalence of the efficacy of oral edaravone compared to 60-mg IV edaravone can be assumed. In addition, edaravone exhibits its efficacy by reducing oxidative stress over a long period of time when administered as multiple doses for 10 or 14 days repeatedly.[6,22] Although the plasma C_{max} of unchanged edaravone after administration of the 105-mg oral suspension exceeded the C_{max} obtained with the 60-mg IV formulation, the difference was only slight and the duration of the higher C_{max} level was short. Therefore, the transient increase in C_{max} with the 105-mg oral suspension compared with the 60-mg IV formulation is unlikely to be clinically significant. The observed slight mean difference in t_{max} of 0.56 hour between the 2 edaravone formulations is also not expected to affect the efficacy of edaravone for the same reason. Therefore, the oral suspension of 105-mg edaravone is predicted to have comparable efficacy to that of the IV formulation of 60-mg edaravone.

The AUC values of the sulfate and glucuronide conjugates after administration of the 105-mg edaravone oral suspension were higher than that of the 60-mg IV formulation but showed no significant differences (<2-fold increase). No safety concerns are expected from this finding, as the safety margin for the metabolites is high enough compared with the exposure limit obtained in the nonclinical toxicity study,[23] and the safety of metabolites at higher concentrations in humans has been confirmed through the clinical development of the 60-mg IV edaravone formulation.[22] Additionally, there were no differences in elimination patterns and relative composition ratios of unchanged edaravone and the metabolites in urine associated with the different administration routes, suggesting no alteration in metabolism after oral administration including first-pass metabolism. Finally, no effects from these differences in exposures of the metabolites on edaravone efficacy are expected, as these metabolites are not pharmacologically active.

The 2 edaravone formulations were well tolerated. The safety profile of 60-mg IV edaravone has been found to be similar to that of placebo in patients with ALS,[27] and there were no new safety concerns with regard to the 105-mg oral suspension resulting from this study.

A clinical study will assess the long-term safety of the 105-mg oral suspension of edaravone (NCT04165824). This study aims to determine whether any safety concerns arise from the finding that the upper limit of the 90%CI for the geometric mean ratio of C_{max} slightly exceeded the bioequivalence limits, and the finding that the AUC values of the metabolites were higher with 105-mg oral vs 60-mg IV administration.

In conclusion, the findings from this phase 1 study in healthy volunteers showed equivalent exposure of the 105-mg oral suspension of edaravone to the 60-mg IV formulation, supporting further investigation of ALS treatment with the 105-mg edaravone oral suspension, including evaluation of long-term safety.

Acknowledgments

The authors acknowledge the subjects who participated in this study and the doctors and staff of the study site including Dr Kenichi Furihata of P-one Clinic, Keikokai Medical Corporation. Tricia Newell, PhD, and Sally-Anne Mitchell, PhD, of Edanz Pharma, provided medical writing support, which was funded by Mitsubishi Tanabe Pharma Corporation.

Conflicts of Interest

All authors are employees of Mitsubishi Tanabe Pharma Corporation, which manufactures and markets edaravone.

Funding

This study was funded by Mitsubishi Tanabe Pharma Corporation.

Author Contribution

H.S. and Y.Na. were involved in study design, data analysis, and interpretation. Y.Ni. and Y.S. were involved in study design, study conduct, and data interpretation. K.Y. was involved in study conduct and data collection. M.H. was involved in study design, conduct, and supervision; and data interpretation. M.M. was involved in study design and conduct. Y.K. was involved in study design and data analysis. K.K. was involved in data interpretation and provided medical expertise. All authors were involved in writing or reviewing the manuscript, and gave final approval of the submitted manuscript.

Data Accessibility Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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