Clinical Therapeutics/Volume xxx, Number xxx, 2022

Original Research

Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Profiles in Healthy Participants

Hidetoshi Shimizu, MPharm[1]; Yukiko Nishimura, MPharm[2]; Youichi Shiide, MSc[2]; Makoto Akimoto, BPharm[2]; Hideaki Matsuda, MEng[2]; Yuichiro Kato, MSc[3]; and Manabu Hirai, MPharm[2]

[1]Clinical Pharmacology Group, Data Science Department, Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; [2]Clinical Research & Development I Department, Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; and [3]Biostatistics Group, Data Science Department, Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan

ABSTRACT

Purpose: The safety and efficacy of intravenous edaravone, a neuroprotectant used for the treatment of amyotrophic lateral sclerosis (ALS), have been shown in clinical trials. An oral suspension of edaravone has been developed, but the food effect on its pharmacokinetic profile has not been evaluated. This study aimed to assess the food effect on the pharmacokinetic profile of edaravone after oral administration and to investigate dosing regimens and administration instructions with different meal intake and timing.

Methods: Data from 3 Phase I clinical studies were used to evaluate the effect of food on the pharmacokinetic profiles of a single dose of edaravone oral suspension. In all 3 studies, participants received a single dose of edaravone with various meal conditions. Healthy Japanese adult male participants (Studies 1, 2, and 3) or female participants (Study 3) aged 20 to 45 years at the time of informed consent were included.

Findings: In Study 1, 6 participants were enrolled and 5 completed the study. Nine and 16 participants were treated in Studies 2 and 3, respectively, and all completed the study. The C_{max} and $AUC_{0-\infty}$ of edaravone were lower when administered 30 minutes after a high-fat meal compared with those in a fasted condition (Study 1). Lower plasma edaravone concentrations (approximately within the first hour) and subsequent lower C_{max} and $AUC_{0-\infty}$ were observed after administration of edaravone 4 hours after a high-fat meal (Study 2) or 2 hours after a low-fat meal (Study 3). The C_{max} and $AUC_{0-\infty}$ of oral edaravone were generally similar and not affected when administered 8 hours after a high-fat meal, 4 hours after a low-fat meal, or 2 hours after a light meal relative to the fasted condition. Administration of edaravone 1 hour before a high-fat meal resulted in no effect on C_{max} or $AUC_{0-\infty}$ relative to the fasted condition. Administration of edaravone in the fed or fasted conditions resulted in a similar urine pharmacokinetic profile.

Implications: Oral administration of edaravone with a meal decreased the plasma concentration of edaravone. Oral administration of edaravone 8 hours after a high-fat meal, 4 hours after a low-fat meal, 2 hours after a light meal, and 1 hour before a high-fat meal showed no effect of food on the PK profile of unchanged edaravone compared with that observed under a fasted condition. ClinicalTrials.gov identifiers: NCT04481750, NCT04481789, and NCT05342597. (*Clin Ther*. 2022; 44:XXX–XXX) © 2022 Elsevier HS Journals, Inc. (*Clin Ther.* 2022;000:1–14.) © 2022 The Author(s). Published by Elsevier Inc.

Abbreviations: AE, adverse event; ALS, amyotrophic lateral sclerosis; FDA, U.S. Food and Drug Administration; LS, least squares; TEAE, treatement-emergent adverse event.

Accepted for publication October 13, 2022
https://doi.org/10.1016/j.clinthera.2022.10.001
0149-2918/$ - see front matter

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

Key words: amyotrophic lateral sclerosis, drug–food interaction, edaravone, food effect, Phase I study.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disorder of the motor neurons that ultimately results in death due to respiratory paralysis.[1] The various symptoms of ALS such as dysphagia, hypermetabolism, respiratory disorders, and difficulty in meal preparation and consumption increase the risk of malnutrition.[2] Malnutrition negatively affects prognosis and quality of life. In patients with ALS, rapid decreases in body mass index and body weight or >10% decreases in body weight compared with the predisease state worsened the prognoses of these patients, with deteriorating nutritional status being associated with a worse outcome (ie, increased mortality).[3–5] Therefore, nutritional intervention for adequate meals and calories in patients with ALS from the early disease stage is important.[6] In addition, as the disease progresses, patients with ALS have difficulties consuming sufficient calories for nutrition during each meal, and thus meals are often divided into several portions and taken frequently; caloric supplements may also be provided. Advanced dysphagia also requires nutritional support with a formula that can be swallowed.

Edaravone is a free radical scavenger that was developed as a neuroprotectant. It was first approved for the treatment of acute ischemic stroke and has been subsequently approved for the treatment of ALS in several countries, including Japan and the United States.[7–9] Its mechanism of neuroprotective activity is through inhibition of phospholipid-membrane degradation by free radicals and protection against damage from oxidative stress.[7] The safety and efficacy of intravenous edaravone have been established in an extensive clinical trial program.[10–17]

To treat ALS, 60-mg intravenous edaravone is administered in cycles, with 14-day dosing periods and 14-day drug-free periods.[8] In the first cycle, patients receive daily 60-minute infusions for 14 days; in subsequent cycles, infusions are given on 10 of the 14 days. This treatment regimen, which results in the need for frequent injections and repeated hospital attendance and caregiver visits, places a large burden on patients, families, and health care providers. To improve this, an oral suspension of edaravone has been developed; it has been approved for the treatment of ALS in the United States[18] and is currently being tested further in several clinical studies.

The pharmacokinetic profile of orally administered edaravone, including possible drug–drug interactions and racial differences, has been investigated in healthy participants[19,20] and patients with ALS (NCT04176224). Oral edaravone is well absorbed, reaching C_{max} within 1 hour. It is converted to inactive sulfate and glucuronide conjugates by sulfotransferase and multiple uridine diphosphate glucuronosyltransferase isoforms via hepatic and renal metabolism and is excreted mainly in urine as the glucuronide conjugate. Increases in exposures of unchanged edaravone (AUC and C_{max}) greater than the dose-proportional increase were observed within a dose range of 30 to 300 mg. No significant drug–drug interactions or racial differences in pharmacokinetic profiles were identified.

Comparable plasma edaravone concentrations were achieved with the 105-mg oral suspension and the 60-mg edaravone intravenous formulation, with an $AUC_{0-\infty}$ that met the bioequivalence acceptance criteria and a C_{max} that was not lower than that of the 60-mg intravenous formulation.[20] Equivalent efficacy based on equivalent plasma exposures between oral and intravenous edaravone can be assumed, as the effects of edaravone are thought to result from the action of edaravone in blood and tissue, including cerebrospinal fluid, to which edaravone is rapidly distributed. The upper limit of the 90% CI for the geometric mean ratio of C_{max} of the 105-mg oral suspension and 60-mg intravenous formulation slightly exceeded the upper limit of the bioequivalence acceptance range; however, it is considered that clinically relevant safety issues will not arise. Based on the qualitative and quantitative similarity in pharmacokinetic profiles of the 2 formulations, both the efficacy and safety that is established for intravenous edaravone should translate to the proposed dose of 105-mg oral suspension.

The food effect on the pharmacokinetic profiles of edaravone (ie, food–drug interaction) had not been evaluated prior to these clinical studies. Given that food intake, theoretically, does not directly affect the pharmacokinetic profiles of intravenously

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

administered drugs, this is not a concern for the currently approved intravenous formulation of edaravone. However, food–drug interaction studies are important for the development of orally administered drugs, as the food effect can have a substantial impact on the safety and efficacy if the pharmacokinetic profiles are altered.[21,22] This is particularly important for edaravone because the pharmacokinetic profile of oral edaravone should be qualitatively and quantitatively similar to that of intravenous edaravone for efficacy and safety, and because in patients with ALS, sufficient caloric and nutritional intake is critical.

Using data from 3 studies (Studies 1, 2, and 3), the present analysis aimed to assess the food effect on the pharmacokinetic profile of edaravone after oral administration and to investigate dosing regimens and administration instructions regarding meal intake, which may be used to avoid food effects on pharmacokinetics.

PARTICIPANTS AND METHODS

Participants

Healthy Japanese adult male participants (Study 1 [NCT04481750], Study 2 [NCT04481789], and Study 3 [NCT05342597]) and female participants (Study 3) who were between 20 and 45 years old at the time of informed consent were included. The main exclusion criteria were current or a history of cardiac, hepatic, renal, gastrointestinal, respiratory, psychiatric, nervous, hematopoietic, or endocrine disease; a history of drug or food allergy; a history of alcohol or drug abuse or dependence; a body mass index <18.0 or >30.0 kg/m^2 or body weight <50 kg; participants who had previously received edaravone; had undergone any surgery known to affect the gastrointestinal absorption of drugs; female and male participants who did not agree to use an effective method of contraception during the course of the study; or female participants with a positive pregnancy test result, those who were pregnant or breastfeeding, or those who planned to become pregnant during the course of the study. All participants provided written informed consent.

Study Design and Treatments

This study analyzed data from 3 clinical studies to evaluate the effect of food on the pharmacokinetic profiles of a single dose of edaravone oral suspension. In all 3 studies, participants received a single dose of edaravone with various meal conditions that were set in reference to the guidance of the U.S. Food and Drug Administration (FDA)[21,22] and with consideration of the lifestyles of patients with ALS. The compositions of the high-fat meal (800–1000 kcal, including 55–65 g fat [500–600 kcal]) and a low-fat meal (400–500, kcal including 11–14 g fat [100–125 kcal]) were based on the FDA guidance, and the light meal (consisting of a caloric solution typically ingested by patients with ALS [~250 kcal]) was based on the lifestyle of patients with ALS. The composition of the edaravone oral suspension has been described previously (Studies 1 and 2[19] and Study 3[20]).

The study design for each of the 3 studies is shown in Figure 1. Each study was a single-center study conducted in Japan. Study 1 was a Phase I study evaluating the pharmacokinetic profile of edaravone oral suspension in healthy adult male participants in the fed or fasted states. All participants experienced both fasted and fed conditions sequentially. For both the fed and fasted conditions, participants fasted (except for water) overnight for at least 10 hours before receiving a single dose of 200-mg edaravone oral suspension. During the fasted state, participants received the study drug and remained in a fasted state until 4 hours after dosing. During the fed state, participants received the study drug after a high-fat meal intake (30 minutes after finishing a high-fat meal). Blood samples were collected predose; 15 and 30 minutes' postdose; and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours' postdose for pharmacokinetic assessment.

Study 2 was a Phase I study conducted in healthy adult male participants that investigated the food effect with administration of edaravone suspension. Three groups of randomized participants received a single dose of 100-mg edaravone (Day 1, Day 4, and Day 7) under each of 3 dosing meal conditions in a 3-way, 3-period crossover fashion: (1) fasted for at least 10 hours and maintaining the fasted state until 4 hours after dosing; (2) dosing 4 hours after consuming a high-fat meal; and (3) consumption of a high-fat meal 1 hour after dosing (administered under a fasted state for at least 10 hours). Blood samples were collected predose; 5, 15, and 30 minutes' postdose; and 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 36, and 48 hours' postdose for pharmacokinetic assessment.

Study 3 was a Phase I food effect study with a crossover design conducted in healthy adult participants. Four groups of randomized participants received 105-mg edaravone oral suspension at 5 dosing periods

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

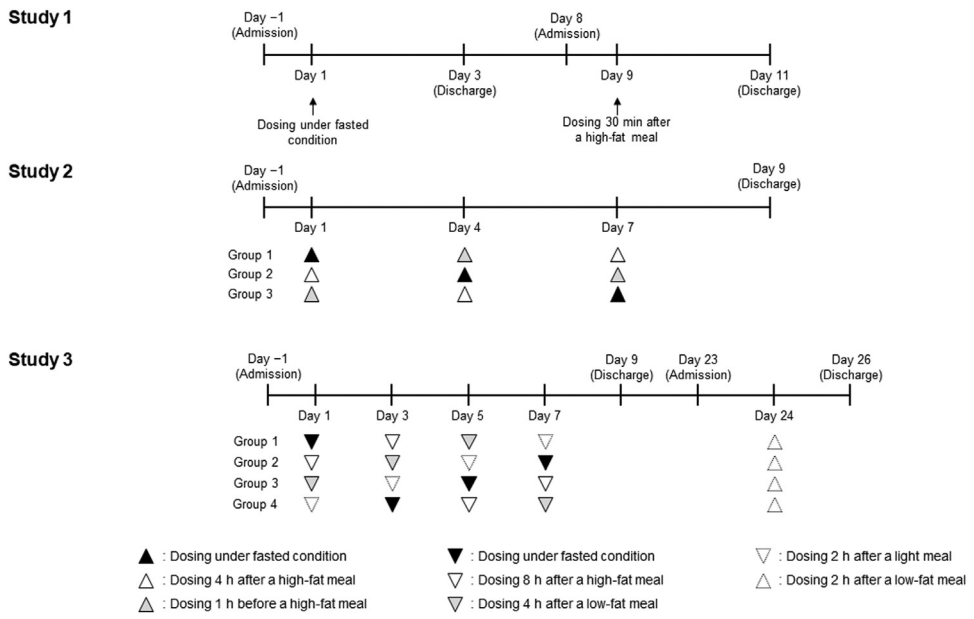

Figure 1. Study design for Studies 1, 2, and 3.

(Day 1, Day 3, Day 5, Day 7, and Day 24) under each of 5 dosing conditions: fasted (for at least 10 hours before dosing), 8 hours after a high-fat meal, 4 hours after a low-fat meal, and 2 hours after a light meal (Ensure Liquid®, Abbott Nutrition, Chicago, IL, USA), which was used as a nutritional supplement in patients with difficulty in taking food orally (eg, patients with ALS), in the first to fourth dosing periods, and 2 hours after a low-fat meal in the fifth dosing period. The meal condition, content, and timing of the postprandial dosing of the fifth dosing period were determined based on the results of the first 4 dosing periods; therefore, time between the fourth and fifth dosing periods was needed to measure drug concentrations and analyze the pharmacokinetic data obtained from day 1 to day 9. All meals, except for the high-fat meal taken at night on the day before dosing (as the dosing condition of 8 hours after a high-fat meal) were consumed after overnight fasting for at least 10 hours. Blood was collected predose; at 5, 15, 30, and 45 minutes' postdose; at 1, 1.5, 2, 4, 6, 8, 10, 12, 24, and 36 hours' postdose; and at 46 hours' (4 hours after a low-fat meal) or 48 hours' (fasted, 8 hours after a high-fat meal, 2 hours after a light meal, and 2 hours after a low-fat meal) postdose (used as the predose of the next dose in the first to third dosing periods) for pharmacokinetic assessment. Urine was collected by voluntary urination until 46 or 48 hours' postdose (as described for blood collection), and by forced voiding before edaravone administration and at 24 and 48 hours' postadministration (as described for blood collection).

The processing and analysis of blood and urine samples and the bioanalytical assays for determination of the pharmacokinetic profile of unchanged edaravone and metabolites in plasma and urine with validated methodology have been described previously.[19,20]

The study protocol for Study 1 was approved by the Institutional Review Board of Medical Corporation Heishinkai OPHAC Hospital and regulatory authorities. The study protocols for Studies 2 and 3 were approved by the Institutional Review Board of P-One Clinic, Keikokai Medical Corporation, and regulatory authorities. Each study was conducted in accordance with the ethical principles originating 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 study protocol.

Outcomes

Results were compared within each study, and pharmacokinetic parameters of edaravone and its

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

metabolites before and after meals were compared with pharmacokinetic parameters under fasted conditions as a control. $AUC_{0-\infty}$, C_{max}, T_{max}, and terminal $t_{1/2}$ were evaluated in all 3 studies. All plasma pharmacokinetic parameters were calculated by using noncompartmental analysis with Phoenix WinNonlin software version 6.3 (Certara, Princeton, NJ, USA). $AUC_{0-\infty}$ was calculated by using the linear trapezoidal method plus last measurable concentration/the exponential rate constant of the terminal phase. The pharmacokinetic parameters were calculated using actual time, with the time of study drug administration being considered 0 hours for all doses. When the same parameter had both observed and predicted values, the observed value was adopted. A drug concentration below the limit of quantitation (<1 mg/mL) was considered as a numerical value of 0. Cumulative urine pharmacokinetic parameters (urinary excretion ratio from 0 to 48 hours) for unchanged edaravone, sulfate conjugates, glucuronide conjugates, and sum of unchanged edaravone and the metabolites were calculated for Study 3. Adverse events (AEs) were monitored for safety and assessed by using the Medical Dictionary for Regulatory Activities version 21.0 (Studies 1 and 2) or version 22.0 (Study 3).

Statistical Methods

The target number of participants was set on the assumption that the number was adequate to obtain results that would meet the study objectives; sample size was not determined statistically. The sample size of Study 2 was assumed based on the findings of Study 1, and the sample size of Study 3 was assumed based on the findings of Studies 1 and 2. The sample sizes for Studies 1, 2, and 3 were 6, 9 (3 per group), and 16 (4 per group) participants, respectively.

Regarding the statistical methods for assessment of food effect used in each study, the parameters C_{max} and $AUC_{0-\infty}$ of unchanged edaravone in plasma were log transformed before analysis. In Study 1, a linear mixed effects model of repeated measurements for log-transformed C_{max} and $AUC_{0-\infty}$ of unchanged edaravone in plasma was used with meal conditions and participants as a factor. In Study 2, a linear mixed effects model was fitted to log-transformed C_{max} and $AUC_{0-\infty}$ of unchanged edaravone in plasma and was used with meal condition, period, and sequence as a fixed effect and participant as a random effect. In Study 3, for the first to fourth dosing, a linear mixed effects model was fitted to log-transformed C_{max} and $AUC_{0-\infty}$ of unchanged edaravone in plasma and was used with meal conditions, sequence, and periods as a fixed effect and participants nested in sequences as a random effect. For the fifth dosing compared with the fasted condition in the first to fourth dosing, a linear mixed effects model for log-transformed C_{max} and $AUC_{0-\infty}$ of unchanged edaravone in plasma was used, with meal conditions and sequence as a fixed effect and participants nested in sequences as a random effect. For all 3 studies, the estimated difference in least squares means and corresponding 90% CI were back transformed to obtain the estimate and CI of the geometric mean ratio of each meal condition to the fasted state. Statistical analyses for assessment of food effect were performed by using SAS version 9.3 or higher (SAS Institute, Inc., Cary, NC, USA).

Absorption profiles of edaravone were investigated by using a deconvolution method based on the plasma concentration–time profiles after administration of edaravone at a dose of 60 mg intravenous or 105-mg oral suspension from a previous study[20] using Phoenix WinNonlin software version 6.3.

RESULTS

Participants

In Study 1, 6 participants were enrolled, and 5 completed the study; 1 participant completed the fasting portion of the study but withdrew because of an AE of conjunctivitis before completing the fed portion of the study. Nine and 16 participants were treated in Studies 2 and 3, respectively, and all completed the study. The demographic characteristics of the study participants are shown in Table I. Studies 1 and 2 included only male participants; Study 3 included both male (75%) and female (25%) participants. Other demographic characteristics were similar among the studies.

Plasma Concentrations and Pharmacokinetic Parameters

Plasma edaravone concentrations over time for all 3 studies are shown in Figure 2. Plasma edaravone concentration was lower, especially around C_{max}, when administered 30 minutes after a high-fat meal compared with that in a fasted condition (Study 1). Lower plasma edaravone concentrations were observed especially approximately within the first hour after administration of edaravone 4 hours after

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

Table I. Demographic characteristics of the study participants. Data are mean (SD) unless otherwise indicated.

Characteristic	Study 1 (n = 6)	Study 2 (n = 9)	Study 3 (n = 16)
Sex			
Male	6 (100%)	9 (100%)	12 (75.0%)
Female	–	–	4 (25.0%)
Age, y	27.0 (4.1)	32.3 (9.1)	30.7 (7.4)
Height, cm	169.6 (3.3)	171.5 (3.0)	169.9 (7.9)
Weight, kg	63.0 (9.2)	67.8 (7.2)	63.1 (8.3)
Body mass index, kg/m^2	21.91 (3.37)	23.08 (2.77)	21.81 (1.77)
Ethnicity, Japanese	6 (100%)	9 (100%)	16 (100%)

a high-fat meal (Study 2) or 2 hours after a low-fat meal (Study 3). Plasma concentrations in other meal conditions were similar to those in fasted conditions.

The plasma pharmacokinetic parameters of unchanged edaravone are shown in Table II. Pharmacokinetic parameters were affected by the consumption of a high-fat meal 30 minutes before edaravone administration (Study 1), with a reduced C_{max} and subsequently reduced $AUC_{0-\infty}$ by ~60% to 80% compared with the fasted condition. When edaravone 100 mg was administered 4 hours after consuming a high-fat meal (Study 2) or 105 mg was administered 2 hours after consuming a low-fat meal (Study 3), the C_{max} and $AUC_{0-\infty}$ were reduced by ~45% and 20% to 25%, respectively, compared with the fasted condition. The pharmacokinetic parameters of 105-mg oral edaravone were generally similar and not affected when administered 8 hours after consuming a high-fat meal, 4 hours after consuming a low-fat meal, or 2 hours after consuming a light meal relative to the fasted condition. Administration of edaravone 100 mg 1 hour before consuming a high-fat meal resulted in no effect on C_{max} or $AUC_{0-\infty}$ relative to the fasted condition.

The plasma pharmacokinetic parameters of edaravone metabolites (sulfate conjugate and glucuronide conjugate) are shown in Table III. Pharmacokinetic parameters (C_{max} and $AUC_{0-\infty}$) of edaravone metabolites after administration 30 minutes after consuming a high-fat meal were decreased compared with the fasted condition, particularly for the sulfate conjugate. However, the magnitude of the reduction was smaller than that of unchanged edaravone (Study 1). These parameters were similar between fed and fasted conditions for Studies 2 and 3, although those parameters of unchanged edaravone were decreased in some fed conditions. Plasma sulfate conjugate and glucuronide conjugate concentrations over time for all 3 studies are presented in Supplemental Figures 1 and Figure 2 (see the online version at doi:10.1016/j.clinthera.2022.10.001), respectively.

Figure 3 shows the result of the assessment of absorption as a percentage of total absorption (bioavailability including first-pass process) for 24 hours. Edaravone was rapidly absorbed, with ~90% of the total absorption over 24 hours having been completed within 1 hour of edaravone administration.

Urine Pharmacokinetic Parameters (Study 3)

Urine pharmacokinetic parameters for unchanged edaravone, edaravone metabolites (sulfate conjugate and glucuronide conjugate), and the sum of unchanged edaravone and sulfate and glucuronide conjugates for Study 3 are shown in Table IV. Overall, administration of edaravone in the fed or fasted condition resulted in a similar urine pharmacokinetic profile.

Safety Profile

In Study 1, four treatment-emergent AEs (TEAEs) were observed in 3 participants. TEAEs were mild or moderate in severity and all were judged to be not reasonably related to the study drug by the investigator. There were no serious AEs or deaths. In Study 2, 2 of 9 participants (22.2%) experienced TEAEs, and one adverse drug reaction (increased alanine aminotransferase level) occurred in 1 participant (11.1%) after being administered edaravone 1 hour

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

Table II. Plasma pharmacokinetic parameters of unchanged edaravone.

Study	Meal Condition	Dose (mg)	T_{max} (h): Median (range)	C_{max} (ng/mL): Mean (SD)	LS Mean Ratio of C_{max} (90% CI)	$AUC_{0-\infty}$ (ng·h/mL): Mean (SD)	LS Mean Ratio of $AUC_{0-\infty}$ (90% CI)	$t_{1/2}$ (h): Mean (SD)
Study 1 (n = 6)	Fasted	200	0.50 (0.25–0.50)	4933 (1268)	—	6313 (1246)	—	9.05 (2.37)
Study 1 (n = 5)	30 min after a high-fat meal*	200	0.50 (0.25–4.00)	899.0 (463.9)	0.175 (0.123–0.250)	2466 (825)	0.387 (0.327–0.459)	5.23 (1.71)
Study 2 (n = 9)	Fasted	100	0.25 (0.25–1.00)	1810 (849.8)	—	1647 (433)	—	9.33 (4.87)
Study 2 (n = 9)	1 h before a high-fat meal*	100	0.50 (0.25–1.50)	1502 (1272)	0.657 (0.379–1.137)	1475 (658)	0.842 (0.697–1.017)	9.65 (5.41)
Study 2 (n = 9)	4 h after a high-fat meal*	100	0.25 (0.25–1.00)	1012 (603.3)	0.522 (0.301–0.903)	1247 (425)	0.737 (0.610–0.891)	7.66 (4.12)
Study 3 (n = 16)	Fasted	105	0.38 (0.25–0.50)	2318 (1229)	—	2165 (673)	—	8.17 (2.29)
Study 3 (n = 16)	8 h after a high-fat meal*	105	0.25 (0.08–0.75)	2525 (1337)	1.083 (0.821–1.429)	2209 (658)	1.025 (0.931–1.128)	7.38 (1.97)
Study 3 (n = 16)	4 h after a low-fat meal†	105	0.50 (0.25–0.75)	2020 (1114)	0.872 (0.661–1.150)	2073 (641)	0.959 (0.871–1.056)	9.05 (5.07)
Study 3 (n = 16)	2 h after a light meal‡	105	0.38 (0.25–1.00)	1898 (865.9)	0.820 (0.621–1.082)	1955 (523)	0.910 (0.827–1.002)	7.31 (4.30)
Study 3 (n = 16)	2 h after a low-fat meal†	105	0.50 (0.25–1.50)	1276 (805.6)	0.536 (0.362–0.794)	1717 (463)	0.801 (0.712–0.901)	11.25 (8.35)

Least squares (LS) mean ratios were calculated as before or after meal/fasted.
*Total 800 to 1000 kcal with 500 to 600 kcal (50% of total calories) from fat based on the FDA draft guidance.
†Total 400 to 500 kcal with 100 to 125 kcal (25% of total calories) from fat based on the FDA draft guidance.
‡Caloric solution that is typically taken by patients with ALS (250 kcal, 250 mL).

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

Table III. Plasma pharmacokinetic parameters for the sulfate conjugate and glucuronide conjugate of edaravone.

Study	Meal Condition	Dose (mg)	T_{max} (h): Median (Range)	C_{max} (ng/mL): Mean (SD)	C_{max} Ratio[a] (%)	$AUC_{0-\infty}$ (ng·h/mL): Mean (SD)	$AUC_{0-\infty}$ Ratio[a] (%)	$AUC_{0-\infty}$ Ratio to Unchanged Edaravone[b] (fold)	$t_{1/2}$ (h): Mean (SD)
Sulfate conjugate									
Study 1 (n = 6)	Fasted	200	1.00 (1.00–1.00)	12,190 (2087)	–	46,393 (10697)	–	7.3	5.93 (1.67)
Study 1 (n = 5)	30 min after a high-fat meal[c]	200	1.00 (1.00–2.00)	7324 (743.2)	60.1	38,768 (4741)	83.6	15.7	5.08 (1.32)
Study 2 (n = 9)	Fasted	100	0.50 (0.50–1.00)	8394 (1609)	–	24,484 (5861)	–	14.9	10.50 (7.67)
Study 2 (n = 9)	1 h before a high-fat meal[c]	100	0.93 (0.50–1.50)	7802 (1556)	92.9	22,689 (6334)	92.7	15.4	7.53 (3.55)
Study 2 (n = 9)	4 h after a high-fat meal[c]	100	0.50 (0.50–1.00)	8152 (1731)	97.1	23,022 (5094)	94.0	18.5	7.55 (2.47)
Study 3 (n = 16)	Fasted	105	0.75 (0.50–0.75)	8456 (2041)	–	24,519 (7243)	–	11.3	6.32 (1.85)
Study 3 (n = 16)	8 h after a high-fat meal[c]	105	0.63 (0.50–1.00)	9024 (2430)	106.7	25,724 (7729)	104.9	11.6	7.16 (2.52)
Study 3 (n = 16)	4 h after a low-fat meal[d]	105	0.75 (0.50–1.00)	8629 (1960)	102.0	24,671 (6077)	100.6	11.9	5.85 (1.18)
Study 3 (n = 16)	2 h after a light meal[e]	105	0.75 (0.50–1.50)	8665 (2362)	102.5	25,903 (8657)	105.6	13.2	6.25 (1.69)
Study 3 (n = 16)	2 h after a low-fat meal[d]	105	1.00 (0.75–1.50)	7986 (2288)	94.4	26,293 (10355)	89.0	15.3	4.91 (1.02)
Glucuronide conjugate									
Study 1 (n = 6)	Fasted	200	0.50 (0.50–1.00)	3507 (157.5)	–	8183 (1283)	–	1.3	4.25 (0.69)
Study 1 (n = 5)	30 min after a high-fat meal[c]	200	1.00 (0.50–2.00)	1893 (357.5)	54.0	7443 (1374)	91.0	3.0	3.76 (0.91)
Study 2 (n = 9)	Fasted	100	0.50 (0.25–1.00)	2391 (507.8)	–	4178 (873)	–	2.5	4.26 (0.38)
Study 2 (n = 9)	1 h before a high-fat meal[c]	100	0.50 (0.50–1.50)	2176 (474.5)	91.0	4099 (637)	98.1	2.8	3.89 (0.79)
Study 2 (n = 9)	4 h after a high-fat meal[c]	100	0.50 (0.50–1.00)	1924 (379.9)	80.5	3557 (879)	85.1	2.9	3.88 (0.55)
Study 3 (n = 16)	Fasted	105	0.50 (0.50–1.00)	2283 (496.2)	–	4054 (791)	–	1.9	4.12 (0.34)
Study 3 (n = 16)	8 h after a high-fat meal[c]	105	0.50 (0.50–1.00)	2209 (645.9)	96.8	3895 (796)	96.1	1.8	4.07 (0.41)
Study 3 (n = 16)	4 h after a low-fat meal[d]	105	0.75 (0.50–1.00)	2283 (486.7)	100.0	4109 (891)	101.4	2.0	4.12 (0.46)
Study 3 (n = 16)	2 h after a light meal[e]	105	0.50 (0.50–1.50)	2141 (548.1)	93.8	3914 (841)	96.5	2.0	4.03 (0.70)
Study 3 (n = 16)	2 h after a low-fat meal[d]	105	0.75 (0.50–1.00)	2031 (608.9)	89.0	4325 (1054)	106.7	2.5	3.67 (0.34)

[a] Ratio of the mean value after food intake to the mean fasting value.
[b] Ratio of the mean $AUC_{0-\infty}$ of metabolites to parent (unchanged edaravone) without consideration of molecular weight.
[c] Total 800 to 1000 kcal with 500 to 600 kcal (50% of total calories) from fat based on the FDA draft guidance.
[d] Total 400 to 500 kcal with 100 to 125 kcal (25% of total calories) from fat based on the FDA draft guidance.
[e] Caloric solution that is typically taken by patients with ALS (250 kcal, 250 mL).

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

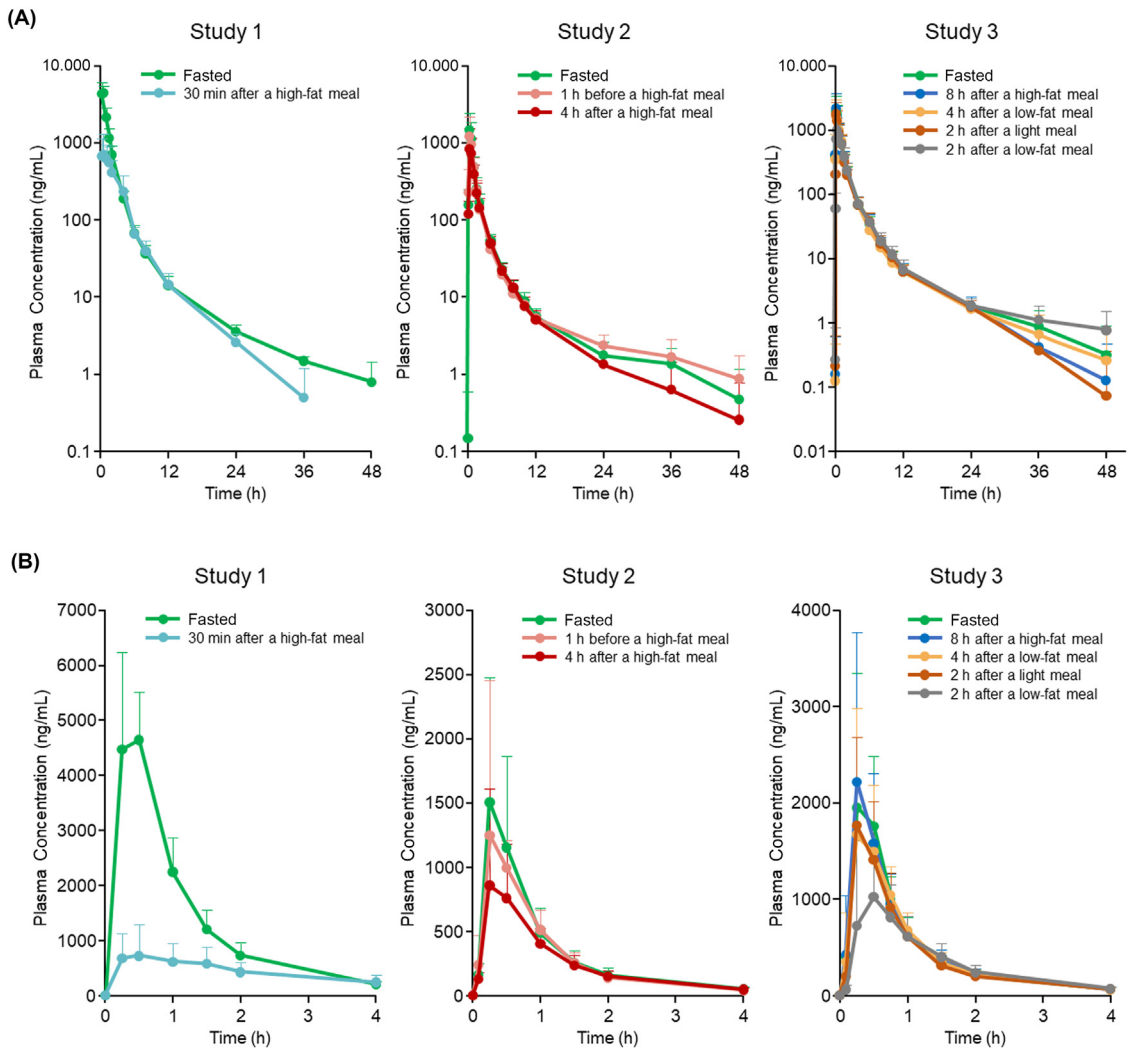

Figure 2. Mean edaravone plasma concentration in fasted and fed states for Studies 1, 2, and 3 shown in a log-linear graph from 0 hours to 48 hours (A) and in a linear-linear graph from 0 hours to 4 hours (B). The error bars represent SD. The x-axis represents time after each dose to show the change in concentration over time.

before a meal. No serious AEs or deaths were reported. In Study 3, one TEAE of urticaria that was moderate in severity was reported; this AE was considered not reasonably related to the study drug by the investigator. No other AEs, adverse drug reactions, or serious AEs were reported.

DISCUSSION

The effect of food (including timing of food consumption, type or caloric intake of meals) on the pharmacokinetic profiles of edaravone was investigated in healthy Japanese participants. The assessments were made by comparing the pharmacokinetic parameters of edaravone administered under several meal conditions versus those under fasted conditions (≥10 hours of fasting). When edaravone was administered 30 minutes after consuming a high-fat meal, 4 hours after consuming a high-fat meal, and 2 hours after consuming a low-fat meal, the C_{max} and $AUC_{0-\infty}$ were reduced by ~80% and 60%, 45% and 25%, and

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

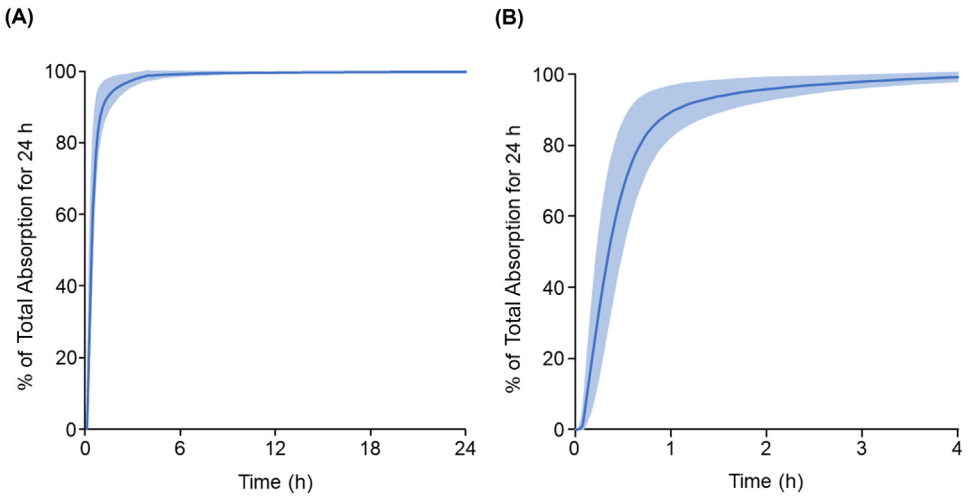

Figure 3. Percentage of total absorption for 24-hour time profiles of unchanged edaravone under fasted conditions from 0 hours to 24 hours (A) and from 0 hours to 4 hours (B). The solid line represents mean values; the light blue shading represents the ranges of the SDs.

Table IV. Cumulative urine pharmacokinetic parameters for Study 3. Values are given as mean (SD).

Meal Condition	$Ae\%_{0-48}$% of Dose			
	Unchanged Edaravone	Sulfate Conjugate	Glucuronide Conjugate	Sum of Unchanged Edaravone and Metabolites
Fasted	0.782 (0.350)	9.13 (8.34)	69.2 (9.4)	79.1 (10.6)
8 h after a high-fat meal*	1.535 (2.505)	8.62 (8.33)	70.3 (9.8)	80.4 (9.2)
4 h after a low-fat meal†	0.936 (0.394)	8.63 (9.22)	68.8 (8.8)	78.4 (9.4)
2 h after a light meal‡	0.945 (0.926)	8.65 (7.25)	73.3 (10.7)	82.9 (7.3)
2 h after a low-fat meal†	1.242 (1.993)	5.85 (6.25)	76.7 (21.3)	83.8 (22.0)

All participants were given 105 mg oral edaravone. $Ae\%_{0-48}$ = urinary excretion ratio from 0 to 48 hours.
* Total 800 to 1000 kcal with 500 to 600 kcal (50% of total calories) from fat based on the FDA draft guidance.
† Total 400 to 500 kcal with 100 to 125 kcal (25% of total calories) from fat based on the FDA draft guidance.
‡ Caloric solution that is typically taken by patients with ALS (250 kcal, 250 mL).

45% and 20%, respectively, compared with when the drug was administered in the fasted condition. These parameters were generally similar in the other fed conditions compared with fasted conditions, such as 8 hours after consuming a high-fat meal, 4 hours after consuming a low-fat meal, 2 hours after consuming a light meal (caloric solution typically taken by patients with ALS), and 1 hour before consuming a high-fat meal. Although administration of edaravone in some fed states decreased C_{max}, T_{max} was generally observed within 0.5 hour of dosing, irrespective of the meal type or timing.

To achieve an exposure of edaravone oral suspension equivalent to that of intravenous edaravone and to

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

ensure that patients can achieve sufficient meal/caloric intake, food effects on edaravone pharmacokinetic profiles should be prevented. To ensure sufficient calories for nutrition, it is especially important to prevent food effects in patients with more advanced ALS because frequent consumption of meals consisting of small portions of food, plus a caloric supplement, are required as the disease condition progresses. The present study identified dosing regimens with no food effect by modifying the timing of edaravone administration relative to food consumption based on the type or caloric content of meals. These dosing regimens can be used to minimize the required fasting duration according to meal type/caloric content, which will be beneficial for patients with ALS.

Given the *in vitro* physiochemical properties of good solubility and good permeability of edaravone,[23] a minimal food effect on its pharmacokinetic profile was expected.[24] However, a notable food effect was observed, especially after edaravone was administered 30 minutes following meal intake. The reason for this notable food effect has not been clearly elucidated; however, a possible cause may be related to metabolism. Plasma concentrations of edaravone metabolites, which are inert, were minimally affected by the food intake scenarios that caused decreases in the plasma concentration and pharmacokinetic parameters of unchanged edaravone. This suggests that the fraction absorbed through the gastrointestinal tract was only mildly affected, given that a reduced fraction absorbed may lead to decreases in the plasma concentration of all edaravone components, including metabolites. Because the concentration of edaravone metabolites decreased very little compared with the concentration of unchanged edaravone, the relative composition ratios of metabolites in the plasma were increased; thus, metabolism could be one potential cause of food effects. Metabolism as a cause of food effects may include nonlinear metabolism associated with altered concentrations of edaravone in the portal vein and subsequently in the liver during first pass, derived from the different rate of absorption caused by meal intake. This is also supported by urinary excretion of edaravone-related components relative to the fasted condition when edaravone oral suspension was administered 2 hours after consuming a low-fat meal. The cumulative urinary excretion ratio of the sum of unchanged edaravone and the metabolites did not differ between these 2 conditions, although the $AUC_{0-\infty}$ of unchanged edaravone decreased by ~20%, suggesting that the fraction absorbed through the gastrointestinal tract was not altered due to meal intake.

The meal condition of administration 30 minutes after finishing a high-fat meal (Study 1) was set as a fed condition with minimal interval (ie, administration just after meal intake). However, the FDA guidance defines the fed condition as a meal intake that is started 30 minutes before administration.[21] In addition, the effect of food intake just before the dosing (ie, administration 30 minutes after food intake) was not investigated with the intended clinical dose of 105 mg. However, a marked decrease in the C_{max} and $AUC_{0-\infty}$ was observed with a preliminary formulation at the dose of 200 mg (Study 1) administered 30 minutes after finishing meal consumption, suggesting that the pharmacokinetic profile of oral edaravone at the intended clinical dose of 105 mg is also affected by food intake just before administration. Thus, edaravone oral suspension should be administered at a sufficient interval before and after meals. The present study showed that sufficient time intervals varied according to the type of meal consumed or the caloric content (Studies 2 and 3). These findings have elucidated several dosing regimens that are suitable to prevent food effects with edaravone treatment.

Administration of 100 mg of edaravone 1 hour before a high-fat meal resulted in a slightly lower C_{max} and $AUC_{0-\infty}$ relative to the fasted condition, although this was not significant. This finding is likely due to variability in the pharmacokinetic data rather than a food effect, as the plasma unchanged edaravone concentration reached C_{max} well before the time the meal was consumed. Evaluation of unchanged edaravone absorption in a fasted state using the deconvolution method indicated that ~90% of the total fraction absorbed (up to 24 hours) occurred within 1 hour of dosing. Therefore, meal consumption 1 hour postdose is unlikely to appreciably alter the pharmacokinetic variables of edaravone.

The present study has some limitations. First, not all causes of the food effect on edaravone pharmacokinetic profiles were clarified in the study. Further research is needed to fully investigate all potential causes of food effects and to understand edaravone pharmacokinetic features in the absorption process. Second, it was not feasible to test all possible meal conditions for

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

food effects on pharmacokinetic profiles. In addition, the meals used in this study did not necessarily match the types of meals consumed by patients with ALS in their everyday life. The definitions of meals used in this study were based on FDA guidance, and the names of meals used in the present study may not be suitable in some countries. For example, the low-fat meal used in this study is similar to a moderate meal as defined in the European Medicines Agency guidance[25] and was also similar to the daily meals, which were not associated with edaravone administration, served at the Japanese facility in Study 3. To ensure sufficient plasma exposures of edaravone, the caloric content and nutritional composition of meals can be used as a guide to select an appropriate dosing regimen. Finally, this study only included healthy Japanese participants. It is noted that no difference has been found in pharmacokinetic features between healthy subjects and patients with ALS (NCT04176224) and between Japanese and Caucasian subjects.[19]

CONCLUSIONS

Oral administration of edaravone with a meal decreased the plasma concentration of edaravone. By adjusting dose timing relative to meal intake according to types of meals, sufficient plasma exposures can be achieved with minimized fasting duration based on the meal type. Oral administration of edaravone 8 hours after a high-fat meal, 4 hours after a low-fat meal, 2 hours after a light meal, and 1 hour before a high-fat meal showed no effect of food on the pharmacokinetic profiles of unchanged edaravone compared with those observed under a fasted condition. These dosing regimens can be used to prevent food effects, providing several options to patients with ALS that will allow them to achieve both plasma exposures of edaravone sufficient for efficacy as well as adequate caloric intake.

DATA STATEMENT

The data sets that support the findings of this study are available from the corresponding author (H. Shimizu) upon reasonable request.

DECLARATION OF INTEREST

All authors are employees of Mitsubishi Tanabe Pharma Corporation. The study sponsor had a role in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication, as all authors are employees of the study sponsor.

ACKNOWLEDGMENTS

This study was funded by Mitsubishi Tanabe Pharma Corporation. H. Shimizu and Y. Kato were involved in the study design and data analysis and interpretation. Y. Nishimura and Y. Shiide were involved in the study design, study conduct, and data interpretation. M. Akimoto and M. Hirai were involved in the study design, conduct and supervision, and data interpretation. H. Matsuda was involved in the study conduct and data collection. All authors were involved in writing or reviewing the manuscript and gave their final approval of the submitted manuscript.

The authors thank all who participated in the study and the doctors and staff at the clinical study sites. The authors thank Sarah Bubeck, PhD, and Michelle Belanger, MD, of Edanz (www.edanz.com) for providing medical writing support, which was funded by Mitsubishi Tanabe Pharma Corporation, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.10.001.

REFERENCES

1. Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med*. 2017;377:162–172. doi:10.1056/NEJMra1603471.
2. Greenwood DI. Nutrition management of amyotrophic lateral sclerosis. *Nutr Clin Pract*. 2013;28:392–399. doi:10.1177/0884533613476554.
3. Dupuis L, Pradat PF, Ludolph AC, et al. Energy metabolism in amyotrophic lateral sclerosis. *Lancet Neurol*. 2011;10:75–82. doi:10.1016/S1474-4422(10)70224-6.
4. Marin B, Desport JC, Kajeu P, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. *J Neurol Neurosurg Psychiatry*. 2011;82:628–634. doi:10.1136/jnnp.2010.211474.

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

5. Shimizu T, Nagaoka U, Nakayama Y, et al. Reduction rate of body mass index predicts prognosis for survival in amyotrophic lateral sclerosis: a multicenter study in Japan. *Amyotroph Lateral Scler*. 2012;13:363–366. doi:10.3109/17482968.2012.678366.
6. Heffernan C, Jenkinson C, Holmes T, et al. Nutritional management in MND/ALS patients: an evidence based review. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2004;5:72–83. doi:10.1080/14660820410020349.
7. Takei K, Watanabe K, Yuki S, et al. Edaravone and its clinical development for amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(suppl 1):5–10. doi:10.1080/21678421.2017.1353101.
8. Mitsubishi Tanabe Pharma America, Inc, a US subsidiary of Mitsubishi Tanabe Pharma Corporation. RADICAVA® (edaravone injection) for intravenous use. 2022. Available from: https://www.radicava.com/pdfs/radicava-prescribing-information.pdf.
9. Mitsubishi Tanabe Pharma Corporation, Japan. RADICUT® (edaravone injection). Prescribing Information, 2022; 1st Edition. Available from: https://www.info.pmda.go.jp/go/pdf/400315_1190401A1023_3_09.
10. Tanaka M, Sakata T, Palumbo J, et al. A 24-week, phase III, double-blind, parallel-group study of edaravone (MCI-186) for treatment of amyotrophic lateral sclerosis (ALS). *Neurology*. 2016;86(suppl 16) P3.189.
11. Abe K, Itoyama Y, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014;15:610–617. doi:10.3109/21678421.2014.959024.
12. Writing Group on behalf of the Edaravone ALS 19 Study GroupSafety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16:505–512. doi:10.1016/S1474-4422(17)30115-1.
13. Kalin A, Medina-Paraiso E, Ishizaki K, et al. A safety analysis of edaravone (MCI-186) during the first six cycles (24 weeks) of amyotrophic lateral sclerosis (ALS) therapy from the double-blind period in three randomized, placebo-controlled studies. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(suppl 1):71–79. doi:10.1080/21678421.2017.1362440.
14. Writing Group on behalf of the Edaravone ALS 17 Study GroupExploratory double-blind, parallel-group, placebo-controlled extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(suppl 1):20–31. doi:10.1080/21678421.2017.1362000.
15. Writing Group on behalf of the Edaravone ALS 18 Study GroupExploratory double-blind, parallel-group, placebo-controlled study of edaravone (MCI-186) in amyotrophic lateral sclerosis (Japan ALS severity classification: Grade 3, requiring assistance for eating, excretion or ambulation). *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(suppl 1):40–48. doi:10.1080/21678421.2017.1361441.
16. Edaravone ALS 16 Study Group. A post-hoc subgroup analysis of outcomes in the first phase III clinical study of edaravone (MCI-186) in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(suppl 1):11–19. doi:10.1080/21678421.2017.1363780.
17. Takei K, Tsuda K, Takahashi F, et al. Post-hoc analysis of open-label extension period of study MCI186-19 in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18(suppl 1):64–70. doi:10.1080/21678421.2017.1365372.
18. U.S. Food and Drug Administration. FDA approves oral form for the treatment of adults with amyotrophic lateral sclerosis (ALS). May 12, 2022. Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-oral-form-treatment-adults-amyotrophic-lateral-sclerosis-als.
19. Shimizu H, Nishimura Y, Shiide Y, et al. Evaluation of pharmacokinetics, safety, and drug-drug interactions of an oral suspension of edaravone in healthy adults. *Clin Pharmacol Drug Dev*. 2021;10:1174–1187. doi:10.1002/cpdd.925.
20. Shimizu H, Nishimura Y, Shiide Y, et al. Bioequivalence study of oral suspension and intravenous formulation of edaravone in healthy adult subjects. *Clin Pharmacol Drug Dev*. 2021;10:1188–1197. doi:10.1002/cpdd.952.
21. Center for Drug Evaluation and Research (CDER), US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: assessing the effects of food on drugs in INDs and NDAs—clinical pharmacology considerations. 2019. Available from: https://downloads.regulations.gov/FDA-2018-D-4368-0016/attachment_1.pdf
22. Food and Drug Administration Center for Drug Evaluation and Research (CDER), US Department of Health and Human Services, Food and Drug Administration. Guidance for industry: food-effect bioavailability and fed bioequivalence studies. 2002. Available from: https://www.fda.gov/files/drugs/published/Food-Effect-Bioavailability-and-Fed-Bioequivalence-Studies.pdf.

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001

23. Watanabe K, Tanaka M, Yuki S, et al. How is edaravone effective against acute ischemic stroke and amyotrophic lateral sclerosis? *J Clin Biochem Nutr*. 2018;62:20–38. doi:10.3164/jcbn.17-62.
24. Wu C-Y, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. *Pharm Res*. 2005;22:11–23. doi:10.1007/s11095-004-9004-4.
25. European Medicines Agency. Guideline on the investigation of drug interactions; 2012. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf.

Address correspondence to: Hidetoshi Shimizu, MPharm, 1-1-1 Marunouchi, Chiyoda-ku, Tokyo 100-8205, Japan E-mail: shimizu.hidetoshi@ma.mt-pharma.co.jp.

Please cite this article as: H. Shimizu et al., Food Effect Study to Assess the Impact on Edaravone Pharmacokinetic Variables in Healthy Participants, Clinical Therapeutics, https://doi.org/10.1016/j.clinthera.2022.10.001